

Regulation of FMD vaccines within the European Union

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Introduction

The EUFMD European Pharmacopoeia Working Group made a proposal for revision of the FMD vaccine monograph (Amadori, 1999; De Clercq, 2000; De Clercq 2001) and presented its reports to Group 15V of the European Pharmacopoeia (Ph. Eur.). EUFMD informed the Immunological Working Party of the Committee for Veterinary Medicinal Products (CVMP) of the European Agency for the Evaluation of Medical Products (EMA) of its activities and proposed a discussion forum including all key players: EMA, EU, EUFMD, OIE, Ph. Eur. and the FMD vaccine producers. The IWP welcomed this initiative and proposed the CVMP to set up an ad hoc group.

In regulatory terms, foot-and-mouth disease (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 in order 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 that there is no authorised medicine for use against the disease concerned and provided that 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 currently 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. 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 setting up by the Committee for Veterinary Medicinal Products (CVMP) of an *ad hoc* group to prepare guidelines on the requirements for FMD vaccines.

The CVMP *ad hoc* group comprises members of the Immunologicals Working Party of the CVMP, of the Research Group of the European Commission for the Control of FMD of the FAO, and of 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 'Position paper on requirements for vaccines

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against foot-and-mouth disease' which will go out for consultation during 2002. The document proposes practical means whereby applicants for marketing authorisations for FMD can meet the requirements of EU legislation. The group has consulted widely with other international organisations to ensure that the draft proposal have wide acceptance. As part of the consultation process it will be necessary for the relevant EU authorities to consider whether or not changes are needed to EU pharmaceutical legislation to cope with the particular technical issues raised by FMD vaccines. 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 have published a revision proposal for this monograph and are currently working to develop a monograph for FMD vaccines for pigs. The CVMP *ad hoc* group has taken account of the revision proposal in preparing the draft guideline and have put forward a number of proposed amendments to the revision proposal for consideration by Group 15V. During the consultation processes for both documents care will be taken to ensure that they remain compatible and complementary.

This paper describes the approach taken in the draft guideline to those features that make FMD vaccines a 'special case' in terms of authorisation. It is important to emphasise that the approach outlined in this document is the outcome of scientific assessment by the *ad hoc* group of the regulatory challenges presented. Whether or not these proposals are ultimately adopted will depend on the outcome of the process of scientific and legal consultation through which the guideline will now progress.

FMD vaccines as a special case

From a regulatory perspective, 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. EU Pharmaceutical legislation is based on the regulatory model that a vaccine comprises a fixed formulation of ingredients including defined amounts, or limits, of one or more antigens. Any change in terms of addition, substitution or removal of an antigen requires a variation resulting in a new authorisation (known as a 'line extension'). The guideline proposes that a slightly amended definition is required in the case of FMD vaccines and that an FMD vaccine should be defined as a formulation of ingredients including defined amounts (limits) of one or more antigens that varies only in the number and types of antigen present. The maximum permitted number and amount of antigens shall be specified in the authorisation in relation to the safety studies presented. This definition is intended to allow an authorisation to cover the potentially large number of different strains of FMD virus which may be included in an authorised product in any combination without each separate combination requiring an individual authorisation. The issue of whether or not this proposed definition is acceptable within current legislation will require further consideration during the consultation process.

The second factor that makes FMD vaccines a special case is the requirement to ensure that there is a mechanism whereby antigens produced from new master seed viruses can be rapidly incorporated into the authorised product. This need will arise in situations where there is an incursion of a 'new' strain of FMD virus against which established, and therefore previously authorised, vaccine strains do not provide protection. The current approval process for a line extension to include a new strain can take up to 210 days which is not an appropriate time frame for response to an FMD outbreak. The guideline therefore considers a number of mechanisms by which this time frame might be reduced.

Quality Requirements

The guideline is underpinned by the assumption that the method of production and the nature of the antigens are identical for all strains of FMD virus to be included in the authorisation and that the strains differ only in their antigenic characteristics. In this way it is possible to consider that vaccine strains, and the antigens produced from them, are themselves individually authorised once they have been shown to meet the quality requirements of the authorisation. In the case of new strains, there may not be sufficient time available to complete the full range of tests for freedom from extraneous agents according to the relevant CVMP guidelines before there is a need to incorporate the antigen into a vaccine for emergency use. In this case it may be necessary to seek a provisional authorisation based on a risk assessment for freedom from extraneous agents until such time as full testing can be completed. This assessment will take into account the risks of contamination at source in relation to the species and country of origin. The guideline specifies that master seed viruses should be treated with an organic solvent to inactivate enveloped viruses and should be inactivated with a first order inactivant. Consideration must also be given to reducing at source any possible risk of contamination with agents responsible for transmissible spongiform encephalopathies.

An area of particular current interest is that of identifying infected animals, whether or not they have also been vaccinated, by means of measuring antibody to one or more of the non-structural (NS) proteins of FMD virus. Manufacturers may therefore wish to provide potential customers with information on whether or not their vaccine induces antibody to NS proteins. Modern FMD vaccines contain purified preparations of virions from which tissue culture components, including NS proteins, have been removed to a lesser or greater extent through the production process of the antigen. 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 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’.

Safety Requirements

The current revision proposal of the European Pharmacopoeia monograph replaces the intradermolingual safety test with a conventional double dose safety test in the most susceptible category of animals using each recommended route of administration. This test is therefore suitable for vaccines adjuvanted with either aluminium hydroxide or oil. The guideline proposes that the safety of an FMD vaccine can be demonstrated by conducting this double dose safety trial using a vaccine containing the maximum amount and number of antigens. Provided that the results of this test are acceptable, then the safety of lesser amounts or combinations of antigens would not need to be individually demonstrated before authorisation. Likewise, when inclusion is sought for a new strain into an existing authorisation, safety studies should be performed with vaccines formulated to contain the maximum proposed amount of the new antigen. The new antigen shall be considered satisfactory in terms of safety provided that the local and systemic reactions seen with the new strain are no more severe than those seen for the established, authorised strains.

Efficacy requirements

The guideline considers in detail the question of efficacy of FMD vaccines in relation to potency. The European Pharmacopoeia monograph for FMD vaccines establishes a minimum potency of 3 PD₅₀ for an FMD vaccine to be placed on the market in the EU and such vaccines are termed ‘standard potency’ in the draft guideline. Published data suggests that there are benefits to be gained in emergency circumstances from the use of higher potency vaccines. Vaccines with higher antigen payloads have been shown to induce protective immunity more rapidly and, possibly, to increase the ‘breadth’ of the immune response in terms of antigenic cover. The guideline proposes that vaccines with a potency of ≥ 6 PD₅₀ could be classified as ‘higher potency’ vaccines. However, there is currently insufficient evidence to define such vaccines as ‘Emergency’ vaccine, as the extent to which standard potency vaccines can induce the same level of protection as higher potency vaccines has yet to be fully evaluated. The guideline highlights the balance that must be drawn between increasing the potency of a vaccine and decreasing the number of doses that can be prepared from a given antigen stock but considers that the final choice of potency should rest with customer

and should be chosen in relation to the epidemiological situation in which the vaccine will be used.

The definitive test for the ability of an FMD vaccine to protect against disease (termed immunogenicity) is established by means of the Ph. Eur. challenge potency test in cattle. The most difficult issue addressed by the guideline is the use of alternative, serological tests to demonstrate the immunogenicity of FMD vaccines. The guideline takes into account the considerable amount of published evidence showing that a good correlation exists between serum antibody titre and protection against FMD in cattle. However, the 'pass level' titre above which cattle may be considered protected depends on a large number of factors including the serotype of FMD virus used for vaccination and challenge, the serological test used to measure antibody and the conditions under which challenge occurs. The European Pharmacopoeia General Text 5.2.7 states that, challenge studies should be conducted using a challenge strain that is different from the strain used for vaccination. However, in the case of FMD, the guideline proposes that there should be an exemption from this requirement and that challenge should be conducted with a strain homologous to the vaccine strain, provided that it induces the required level of clinical signs in the challenged, unvaccinated controls. The results of a challenge study with a homologous strain provide information on the quality of the antigen and the vaccine in terms of their ability to induce protection against the most relevant antigenic strain. From the customer's perspective however, it may be necessary to conduct additional trials to establish if the vaccine strain also protects against field strains relevant to their particular situation.

In order for a new strain to be considered for inclusion within an authorisation the manufacturer should conduct full potency challenge tests in cattle with a satisfactory result demonstrating that a vaccine blended with a defined amount of antigen has a potency of at least 3 PD₅₀. The revision proposal for the European Pharmacopoeia monograph proposes that subsequent batches can be released on the basis of a serological test in cattle demonstrating that the antibody levels induced by a test batch are not significantly less than those induced by at least three batches shown to be potent by challenge in cattle. The proposal also requires that the serological test used is fully validated and that a satisfactory correlation has been shown between the results of the serological test and protection in cattle. The guideline proposes conditions that should apply in order to reduce the amount of testing required to establish a suitable correlation between the two tests and a pass level for a particular strain. The test to be used shall be the virus neutralisation test using as antigen the vaccine strain for which a serological pass level is being sought. The divided dose challenge study shall show a graded response and at least some animals vaccinated with lower doses shall not be protected. Provided these criteria are met only a minimal number of challenge tests, possibly as few as one, should be required to establish a titre corresponding to the minimum 'pass level' associated with a vaccine having a potency of at least 3 PD₅₀. This pass level can then subsequently be used for all vaccines containing the same or greater amounts of the given antigen, irrespective of the other antigens with which the particular vaccine under test is formulated.

If the proposal to accept the use of serological alternatives to potency testing in cattle is accepted, there will be a greater need for standardised reference sera for FMD serology. The European Department for the Quality of Medicines of the European

Pharmacopoeia has recently undertaken to coordinate a project to produce, evaluate, store and distribute such sera in relation to potency testing of FMD vaccines. Manufacturers may, of course, use serological tests other than the virus neutralisation test but in this situation the test must be fully validated and the correlation between titre and protection established for each antigen and each combination of antigens included within the authorisation.

In terms of the other efficacy parameters of FMD vaccines, the claims made shall reflect the data presented in terms of duration of immunity and reduction of infection, mortality and/or clinical signs. Immunogenicity shall be demonstrated for each species for which an indication is sought. In general, for strains which are virulent in all FMD-susceptible species, batch potency shall be demonstrated in cattle. However, for strains which have a particular virulence and tropism for a species other than cattle e.g. pigs, batch potency shall be demonstrated in the most relevant species. The *ad hoc* group does not consider there is a need to develop a specific monograph for FMD vaccines for sheep and awaits the outcome of the work of Group 15V on the development of a monograph for FMD vaccines for pigs.

Conclusions

In general, the majority of the requirements that apply to all immunological veterinary medicinal products apply equally well to FMD vaccines. There are however some unique features of the disease and vaccines used against it that require a different approach to fulfilling the requirements of the relevant legislation if authorisation of FMD vaccines is going to become routine within the EU rather than an exception. Recent policy changes in terms of how FMD outbreaks should be controlled make vaccination more likely and recent experience suggests that the public and the farming industry would expect any vaccine that is used to be fully authorised. The guidelines currently being prepared propose possible solutions to many of the technical challenges presented by FMD vaccines and it is to be hoped that after the consultation period they will provide valuable advice to manufacturers hoping to place FMD vaccines on the market within the EU.

References

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