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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

**POSITION PAPER ON
REQUIREMENTS FOR VACCINES AGAINST
FOOT-AND-MOUTH DISEASE**

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Background

This draft position paper has been prepared by an *ad hoc* group of the Committee for Veterinary Medicinal Products (CVMP) comprising representatives of the Immunologicals Working Party of the CVMP, of the Office Internationale des Epizooties (OIE, World Organisation for Animal Health), of the European Pharmacopoeia and of the Research Group of the Standing Technical Committee of the FAO European Commission for the Control of FMD. Representatives of DG SANCO and DG Enterprise of the European Commission and of European manufacturers of FMD vaccines acted as invited observers and assisted in its preparation.

This position paper considers the scientific issues raised by FMD vaccines and proposes methods that can be used to demonstrate that vaccines meet the necessary technical standards such that they are suitable for authorisation. The paper does not consider in detail how well these technical standards fall within the existing legislative framework. FMD vaccines, like human influenza vaccines, represent a 'special' case in terms of the need for rapid and constant change in the strains included and therefore do not fit well within the general regulatory model for vaccines.

Rationale for the Position Paper

Directive 2001/82/EC requires that, with only minor exceptions, all veterinary medicinal products that are placed on the market in the European Union (EU) must hold a marketing authorisation and lays down the requirements that veterinary medicinal products, including immunological veterinary medicinal products (IVMPs), must meet to be granted such a marketing authorisation (MA). Exceptional deviations to these general provisions are laid down in particular in Articles 7 and 8 of the said directive. Article 7 permits a Member State, 'where the health situation so requires', to authorise the use of a vaccine on its national territory provided that the product holds a marketing authorisation compliant with that Directive in another Member State. Article 8 permits Member States provisionally to allow use on their territory of a product without an authorisation in the event of a 'serious disease epidemic' provided that no suitable authorised product is available for the disease concerned and provided that the Commission is informed of the detailed conditions of use. The terms 'health situation' and 'serious disease epidemic' are not further defined but are taken to include an outbreak of a disease which is both severe in terms of animal welfare and has the potential for rapid spread, such as the diseases classified under 'List A' by the Office International des Epizooties (OIE) e.g. Foot-and-Mouth disease (FMD), Bluetongue, and rinderpest. Despite these exceptional provisions, there is no reason why the majority of issues related to authorisation of FMD vaccines cannot largely be dealt with in 'peace time' such that Competent Authorities have access to FMD vaccines authorised on their territory in the event of an emergency. If this were the case, there would then be no need to resort to the emergency provision of Articles 7 and 8.

The amendments introduced to Regulation 2309/93 (now Regulation 726/2004) permit vaccines used as part of Community control measures to be authorised through the centralised procedure. Current and future EU policy on the control of FMD places emphasis of the use of vaccines as part of a vaccinate-to-live policy rather than on traditional methods of 'stamping out' or suppressive vaccination (vaccination-to-kill). All of these factors reinforce the need for authorisation of FMD vaccines within the EU. The objective of this position paper is to clarify the requirements that must be met for an FMD vaccine to obtain an MA and to be released as an authorised product.

As the EU is classified as free from FMD, and as routine prophylactic vaccination against the disease is prohibited by legislation, vaccination against FMD in the event of an outbreak is likely to affect only a limited number of animals for a short period of time. Such use could therefore be considered to be a 'minor use' indication as defined in the paper 'EMA/CVMP/477/03-consultation - Position Paper regarding availability of Products for Minor Uses and Minor Species (MUMS)'. Likewise, several of the species which may be vaccinated are classified as 'minor species' as defined in this paper, due to their low numbers within the EU (e.g. goats, buffaloes, zoo species). This guideline, and the requirements contained herein, should therefore be considered in conjunction with Position Paper EMA/CVMP/477/03- Consultation, and future developments in MUMS policy within the EU.

POSITION PAPER ON REQUIREMENTS FOR VACCINES AGAINST FOOT-AND-MOUTH DISEASE

INTRODUCTION

SCOPE OF THE POSITION PAPER

In addition to the requirements of the relevant EU Directives/Regulation and guidelines, the general monograph 'Vaccines for Veterinary Use' (01/2004:0062) and the specific monograph 'Inactivated FMD vaccines for ruminants' (01/2002:0063) of the European Pharmacopoeia (Ph. Eur.) lay down the minimum requirements and standards that FMD vaccines must meet to be eligible for authorisation in the EU.

This position paper considers those aspects of production and use which are unique to FMD vaccines and which are supplementary to the scope of the European Pharmacopoeia. Where relevant, the position paper clarifies the requirements of the relevant European Pharmacopoeia monographs and defines additional requirements that should be met for an FMD vaccine to be considered as suitable for use within the EU. **This position paper should therefore be read in conjunction with the relevant Ph. Eur. monographs, and any subsequent revisions published by the EDQM, as the requirements detailed in these monographs are not repeated here but are essential to any consideration of the quality of FMD vaccines.**

DEFINITIONS

Due to the particular nature of FMD vaccines, and the way in which they are manufactured, it is necessary to define precisely certain terms as they are used within the context of this position paper. Where possible, the terms listed in Appendix XV to Ph. Eur. general text 5.2.1 have been used and these have not been repeated here. The descriptions below specify more precisely how the Ph. Eur. definitions (given in *italics*) have been interpreted within these guidelines for the specific case of FMD vaccines.

Established vaccine strain: A **master seed virus** (MSV) that has been used in the production of FMD vaccines for sufficient time that it has been fully antigenically (and possibly genetically) characterised, and which has been fully tested for freedom from extraneous agents in compliance with these guidelines.

Final antigen lot: A defined mixture of **intermediate antigen lots** that is used to formulate an **FMD vaccine**. **Trial blends** are formulated such that they are truly representative of the final antigen lot in terms of the relative amounts of the various intermediate lots present. The intermediate lots may be physically mixed before storage or may be stored individually and then thawed and blended at a fixed and defined ratio.

FMD antigen: antigen derived from a defined MSV that is included on an authorisation for an FMD vaccine

FMD antigen bank: A set of final antigen lots that is stored for rapid formulation into vaccine in the event of an outbreak.

FMD vaccine: a fixed formulation of adjuvants and excipients that contains defined amounts (limits) of one or more FMD antigens and that varies only in the number and types (serotypes, strains) of FMD antigen present. (n.b. this contrasts with the definition of a 'conventional' vaccine which can be defined as a fixed formulation of adjuvants and excipients containing defined amounts (limits) of one or more antigens and for which the substitution, addition or deletion of an antigen requires a new authorisation).

Immunogenicity: The term is used here as it is in the European Pharmacopoeia to mean the ability of a vaccine to induce a protective immune response, as demonstrated during the licensing procedure.

Intermediate antigen lot: Concentrated, purified, homogeneous, monovalent antigen derived from one or more *monovalent pooled harvests*.

Marketing authorisation for an FMD vaccine: In addition to the normal requirements of a marketing authorisation for an immunological veterinary medicinal product within the EU, an authorisation for an **FMD vaccine** (see above) will specify (i) the **FMD antigens** that may be formulated into the vaccine (ii) the maximal amount and number of antigens that may be included (iii) a quantitative and qualitative description of the other components (excipients, adjuvants) present in the vaccine. A separate authorisation will be required for each FMD vaccine produced by a manufacturer.

Master Seed Virus: A viral stock preparation that complies with the Ph. Eur. definition of a *master seed lot* for which the origin is defined in the authorisation. In the case of FMD virus there are certain well established vaccine strains (e.g. O Manisa, A Iraq) that have been used for many years by several different manufacturers. Manufacturers holding MSVs of these established vaccine strains should fully document the origin and history of their particular MSV.

New vaccine strain: A MSV produced from a strain of virus isolated from the field which has been antigenically (and possibly genetically) characterised to a sufficient extent to conclude that it differs sufficiently from established vaccine strains to warrant evaluation as a new vaccine strain. This guideline details the minimum requirements that should be met for antigen from a new vaccine strain to be used in an FMD vaccine.

Trial blend: An FMD vaccine that is formulated from an intermediate or final antigen lot in the manner described in the authorisation such that it is representative in all respects, and particularly in terms of antigen content, of the final vaccine to be released.

GENERAL COMMENTS

Annex 1, Title II, Part 7 D (Safety) and Part 8 D (Efficacy) of Directive 2001/82/EC requires that applicants shall submit the results of field trials in support of laboratory trials, unless justified.

In view of the prohibition on routine FMD vaccination within the EU, and in line with the CVMP Guideline on Field Trials for Veterinary Vaccines, provided that adequate data is provided on the safety and efficacy of the vaccine under laboratory conditions, the submission of field trials data shall not be required for the purposes of obtaining an authorisation for an FMD vaccine within the EU. Where possible, manufacturers should submit data on the safety and efficacy of FMD vaccines in the field but it is recognised that this information is likely to be considered only as supporting data due to the difficulties in conducting field trials to the required quality standards when the vaccine is used in emergency situations within or outside the EU.

QUALITY REQUIREMENTS

FMD vaccines as a 'special case'

Vaccines against FMD represent a 'special case' in terms of authorisation in that the technology has now been available for over twenty years to store stocks of concentrated, inactivated antigen that can rapidly be formulated into vaccine in the event of an outbreak. The production and testing of trial blends from stored antigens in advance of need can ensure that any vaccine produced at a later date will meet the requirements of the Ph. Eur. in terms of quality, safety and efficacy. The Ph. Eur. monograph 'Foot-and-mouth disease (ruminants) vaccine (inactivated)' is unique in that it contains a special provision to allow Competent Authorities to release vaccine in the event of urgent need, provided that a trial blend representative of the vaccine to be released has been tested with satisfactory results and provided that the various components of the final blend have passed sterility tests.

Several features of the FMD virus and the disease it causes require special consideration in terms of marketing authorisation requirements. First, there is a need to ensure that provision is made to add or replace new strains rapidly into authorised vaccines in the event of the incursion of a new field strain against which none of the currently available vaccine strains are able to confer immunity. In the case of the EU, this risk is more than a theoretical hazard as there have been several instances in the recent past where Europe has been threatened or actually exposed to strains of FMD virus not previously encountered in this region before. Second, there is the range and diversity of serotypes (7) and strains (many for each serotype) of FMD virus that circulate and co-circulate in endemically infected areas. Current guidelines require that the safety and efficacy of all antigens, and all possible combinations of antigens, are individually demonstrated before inclusion within a marketing authorisation. Such a requirement is impractical for FMD vaccines where manufacturers may need to include within the scope of their authorisation any of up to 20 or more strains, and may need to formulate vaccines containing different combinations of strains. In the case of FMD vaccines in particular, this requirement may also be considered excessive in view of the essentially similar nature of the antigens once inactivated, the assurance that is provided by the application of GMP that all batches of antigen are produced to a consistent standard, irrespective of the actual seed strain used, and the well established correlation that exists between serum antibody and protection against challenge in cattle (see section on Potency for details).

Requirements for manufacture

Unless justified, vaccines authorised in the EU should be used. In compliance with article 8 of Directive 2001/82/EC, recourse can only be taken to use unauthorised products where no authorised product is available for the condition concerned. In the case of vaccines manufactured in third countries, the manufacturing facilities should either be subject to inspection by the Competent Authorities of a Member State of the EU or should be certified as compliant with the requirements of Good Manufacturing Practice (GMP) by the Competent Authority of a third country where a mutual recognition agreement is in operation between the EU and the third country in which the vaccine is manufactured.

The quality requirements of the Ph. Eur. monograph 'Inactivated FMD vaccines for ruminants' should apply in terms of production, inactivation and quality control of FMD vaccines and are not repeated here.

Selection and use of vaccine strains

1. Established vaccine strains

Manufacturers of FMD vaccines need to maintain the option to include within their vaccines, one or more of a large number of possible vaccine strains. In the great majority of outbreaks an adequate degree of protection can be provided by vaccines formulated to contain one or more of the established vaccine strains of which manufacturers hold stocks for use on a routine basis. These established vaccine strains have usually been selected over an extended period on the basis that they are highly immunogenic and, generally, that the immunity they induce is broadly reactive against a wide range of field strains. Vaccine containing these strains can therefore often be used over a wide geographical area and there is frequently no need to develop a 'new' vaccine strain when there is an incursion of a new, but antigenically related, strain of FMD virus.

Established vaccine strains are generally prepared and stored in advance of need. For them to be included on an authorisation, the requirements in terms of quality (identity, freedom from extraneous agents, inactivation etc.) are those described in the relevant general guidelines and monographs. As for any other MSV, testing against all agents listed in the table of extraneous agents included in Volume 7B of the Rules governing Veterinary Medicinal Products in the European Community, is not required, provided that an appropriate justification can be provided. For a manufacturer to use antigen of an established vaccine strain in the formulation of an authorised FMD vaccine, the respective MSV must be included on the authorisation following submission of an appropriate dossier to the competent authority.

2. New Vaccine Strains

2.1 Derivation and characterisation

In the case of incursion of a new strain that is antigenically distinct from existing vaccine strains, it may be necessary for a manufacturer to develop a new vaccine strain from a representative field isolate. Where necessary, collaboration with a regional reference laboratory recognised by the FAO &/or the OIE, or with the FAO World Reference Laboratory for FMD at the Institute for Animal Health, Pirbright, should be carried out to ensure that the new field strain is adequately characterised. As classic 'subtyping' is now rarely carried out, strains should be antigenically characterised by means of comparison with other established vaccine strains and possibly field strains using cross neutralisation tests ('r' values) or other suitable physicochemical means (e.g. ELISA). Where possible, genetic sequence analysis should be carried out to determine the phylogenetic relationship between the candidate vaccine strain and other strains of the same serotype but this should not be a requirement for acceptance as a new vaccine strain. Selection of new vaccine strains is generally a commercial issue under the control of the manufacturer. However, where possible, a new vaccine strain should be selected by comparing the antigenic properties and growth characteristics of a number of field strains. The strain selected as the vaccine strain should be antigenically typical of isolates recovered from the outbreak from which it is derived and should be adapted to growth in suspension cell culture. Manufacturers are encouraged to submit samples of new master seed viruses to recognised reference laboratories.

2.2 Freedom from extraneous agents

Wherever possible, the exact source of the isolate should be known and recorded (location, species, type of material) and consideration should be given to minimising at source the risk of transmission of transmissible spongiform encephalopathy agents (TSEs) in accordance with the relevant CVMP guideline. A procedure involving the use of organic solvent(s) which has been validated for the inactivation of enveloped viruses must be applied to the MSV before storage.

Before the new MSV, and Working Seed Viruses (WSV) derived from it, can be accepted as an established MSV, full compliance should be demonstrated with the relevant guidelines to demonstrate freedom from possible contamination with extraneous agents using both general and specific tests. Delays in demonstrating that a new MSV is free from all possible extraneous agents may occur due not only to the time taken to raise the specific antisera necessary to neutralise the new strain for use in the general tests for extraneous agents but also to the time taken to conduct several of the specific tests that require specialised techniques. Therefore, in emergency situations where there is insufficient time to complete full testing of the MSV/WSV, provisional acceptance of the new strain should be on the basis of a risk analysis of the possibility of contamination of antigen produced from the new MSV/WSV with extraneous agents. This risk assessment should take into account the fact that a validated procedure to inactivate enveloped viruses must be used when establishing the MSV and that Ph. Eur. monograph 0063 requires that FMD viral cultures must be inactivated using an inactivant with first order kinetics. In practice, this may mean that little additional testing is considered necessary. As an example, Appendix 1 lists relevant viruses of cattle that are inactivated by lipid solvents and/or aziridines, together with information on whether or not they can be detected using the general and/or specific tests. In this case, only adenoviruses and papilloma viruses may not be inactivated by the treatments applied and, of these, only adenoviruses are likely to present a significant risk. However, the risk of contaminating the production facilities with an exotic extraneous agent present in the seed material must also be borne in mind.

In order to accelerate the release of batches of vaccine formulated to contain new vaccine strains, it may be acceptable for batch potency testing to be carried out using a vaccine formulated using an **intermediate antigen lot** pending production of all of the batches of antigen that are intended to constitute the **final antigen lot**. This will allow the potency of antigen derived from a new MSV/WSV to be determined whilst the manufacturer continues to build up stocks of this new antigen. In emergency situations this result may be adequate for the purposes of release of vaccine made from the final antigen lot, provided that all of the intermediate lots that make up the final lot have been manufactured in the manner described in the authorisation and provided that the vaccine formulated from the final antigen lot contains not less than the amount of antigen used in the trial blend and that

this amount is not greater than the maximum antigen content permitted in the authorisation. This provision is not available for vaccines for routine use where testing should be performed with a trial blend prepared using antigen from the final antigen lot.

Storage conditions

Studies have shown that concentrated antigen stored at low temperature, preferably over liquid nitrogen, remains potent for many years. There is currently insufficient data to predict for how long an antigen will remain potent when stored under particular conditions. As part of the authorisation procedure, manufacturers should validate the storage conditions, and the period for which antigens are stored, by means of studies of representative antigens and of vaccines formulated from them. Manufacturers should demonstrate that vaccine formulated from the stored stocks pass the required batch release tests and have an appropriate shelf life. In the case of antigen banks, bank holders may seek an assurance that the antigens held in store on their behalf remain potent. In such cases bank holders may require periodic tests to be conducted to ensure that the biochemical and antigenic characteristics of the antigen stocks have not deteriorated to an extent sufficient to affect the potency of a vaccine made from them. The following timetable of tests is proposed as suitable for validation and re-validation of stored antigens.

Time	Test
On receipt (year 0) and every 5 years thereafter	146S quantification* Potency test in cattle which, at the discretion of the bank holder, may be a 'truncated' test** to demonstrate that the minimum potency of the vaccine remains greater than the minimum requirement or may rely on serological techniques where potency has been adequately correlated with immunogenicity for the antigen concerned (see section on Potency for detail)
Years 2 and 4, and immediately before formulation if the need arises	146S quantification
Every 5 years	Evaluation of all data for the preceding 5 years to assess need to replace antigen

* Other physiochemical tests such as SDS-PAGE have been used to evaluate integrity of VP1 but are not sufficiently validated for routine use.

** In a truncated test all animals in the next lower volume group are assumed to have not been protected. The test therefore gives an artificially low PD₅₀ value but reduces the number of animals required.

Adjuvants

To obtain a Marketing Authorisation any pharmacologically active ingredient, including adjuvants or excipients, used in the formulation of an FMD vaccine must be included in one of the Annexes to Directive 2377/90 establishing its status with regard to residues in products derived from food producing species.

Current FMD vaccines contain as adjuvants either oils or aluminium hydroxide. Oil adjuvanted vaccines have been shown to be effective in both ruminants and pigs and are therefore well suited as vaccines for emergency use. Vaccines adjuvanted with aluminium are less effective in pigs and would not therefore generally be suitable when vaccination of pigs might be part of an emergency vaccination program.

"Differentiation" of infection from vaccination in FMD

Serological tests have been developed to identify animals which have been infected with FMD virus, whether or not they have also been vaccinated. These include tests that rely on the detection of antibodies to the non-structural (NS) proteins of FMD virus as evidence of viral replication in animals that have been exposed to live, replicating virus. Current FMD vaccines contain semi-purified preparations of virions from which it is possible to exclude the majority of NS proteins meaning that they may induce little, if any, antibody to NS proteins. Exploitation of this differential antibody response has loosely been termed 'differentiation' of infection from vaccination, although this is in

fact a misnomer as the two states (infected/vaccinated) are not mutually exclusive in FMD. Under circumstances where it is envisaged that vaccinated animals will be permitted to live, tests like those specific for NS antibody are likely to be used extensively in future to identify vaccinated herds that have been exposed to FMD virus and which might therefore represent a residual source of infection. Manufacturers may therefore wish to provide information to users that their vaccines do not induce antibody to one or more NS proteins so that they can be used, in conjunction with an appropriate diagnostic test, as part of an emergency vaccination program to ensure that vaccination does not interfere with the identification of infected animals. There is therefore a need to establish quality criteria for such information to be provided to the users.

Quality requirements in support of information related to non-structural proteins

Manufacturers should supply data to substantiate information provided on the Summary of Product Characteristics (SPC) that a vaccine does not induce antibody to one or more NS proteins. To support such information;

- (i) the manufacturing process should include one or more steps to purify the virus from cellular or other contaminants, including NS proteins, that are produced during virus growth in cell culture. As part of the authorisation dossier, the manufacturer should present data from immunochemical tests such as SDS-PAGE, immunoblotting, or some form of competitive based assay to demonstrate that the purification process reduces the level of NS proteins in the final purified, concentrated antigen. However, it is unlikely that any purification process can completely remove NS proteins and there is currently no method of predicting the immunogenicity of any proteins remaining. Therefore demonstrating that the vaccine does not induce significant levels of NS antibody in immunised animals currently represents the only means of supporting information on the SPC relating to NS antibody.
- (ii) the manufacturer should conduct a test to demonstrate that repeated immunisation of one or more of the indicated species with vaccines formulated to contain the maximum permitted amount and number of antigens does not result in seroconversion to NS proteins. Such a test should be required to be conducted at least once for each FMD vaccine (as defined above) for which information is provided (i.e the information relates to the formulation of both adjuvants and antigens together and not to the antigens alone). In order to reduce the use of animals, it may be possible to conduct this test in the animals used for demonstrating the safety of the administration of a single dose, an overdose and a repeat dose in Part III of the application dossier. A recommended immunisation and testing program is as follows;

Prior to Day 0: Collect a sample of blood from a minimum of 10 animals to verify freedom from antibody to FMD virus structural and non-structural proteins. The animals should have no history of exposure to FMD, should not have been previously vaccinated and should be free of non-specific antibody to FMD virus NS antibodies.

Day 0: Administer to a single site a minimum of two doses of a vaccine containing the maximum permitted amount of antigen of each of the maximum permitted number of antigens (i.e. if the authorisation permits up to 15ug of up to four different antigens then the vaccine should contain at least 15ug of each of at least four different antigens)

Day 14-28: Administer a second, identical injection after the interval recommended in the basic vaccination schedule, usually two to four weeks

Day 42 onwards: Administer a third, identical injection between a minimum of one and a maximum of six months after the second injection.

Day 56 onwards: Collect serum samples between two and four weeks after the last vaccination and test for antibody to NS proteins. The antibody levels against specified NS proteins should be lower than those considered as positive in a validated test.

- (iii) manufacturers may use alternative immunisations and testing schedules provided that they can justify that the schedule used is the most likely to induce an antibody response to NS proteins
- (iv) the manufacturer should use a test that has been adequately validated and, where possible, one that has been recognised by an international organisation such as Office International des Epizooties (OIE). In the absence of internationally recognised standards for NS antibody serology, the manufacturer should justify the validation performed to the satisfaction of the competent authority by reference to published data, by independent validation of the test by an internationally recognised FMD reference laboratory and/or by conducting suitable 'in-house' validation studies.

Where possible, the data from experimental animals should be supported by field data derived under actual conditions of use. Data available to date indicate that some animals respond particularly well to some NS proteins but not to others and information on the prevalence of such animals can only be derived from field data. As stated under General Comments, this type of field data is considered as supportive rather than obligatory as it is likely to be generated under relatively uncontrolled conditions.

Care needs to be taken to ensure that the product information provided by the manufacturer is fully supported by the data presented. The test(s) used to detect antibody to NS proteins should always be indicated on the SPC together with the conditions under which lack of immunogenicity was proven (e.g. number of vaccinations, potency and valency of the vaccine, intervaccination interval). This will enable Competent Authorities to make an informed choice of the NS antibody test to be used as part of a surveillance program when NS antibody testing is to be included in a control strategy that involves emergency vaccination. As Competent Authorities for marketing authorisation of vaccines, have no competence in the EU with regard to diagnostic tests, it is inappropriate for manufacturers to propose claims related to 'marker' vaccines or 'differentiation of infection from vaccination' in Section 5 of the SPC. Freedom with respect to NS proteins is a quality issue and therefore the information provided should be restricted to defining precisely the nature of the immune response induced under Section 4 of the SPC 'Immunological Properties'.

Formulation in relation to use

FMD vaccines can be used either for routine, wide scale prophylaxis in advance of any particular threat or for emergency use to prevent, control or contain an actual or potential incursion of disease. FMD vaccines should be formulated for their specific purpose and may be classified as either 'standard' and 'higher' potency vaccines.

Standard Potency vaccines

Standard potency vaccines are formulated to contain sufficient antigen to ensure that they meet at least the minimum potency requirement of the Ph. Eur. (currently 3 PD₅₀). Formulation of stored antigens into vaccines of standard potency has the advantage that the greatest number of animals can be immunised with the antigen available. Standard potency vaccines are well suited for routine prophylaxis in which case solid immunity at a population level depends on the regular and repeated administration of the vaccine as part of a national or regional program.

Higher potency vaccines

Vaccines formulated such that the potency is in excess of the minimum requirement (e.g. by incorporating increased amounts of antigen) have particular features that make them well suited to emergency use over a limited area in the form of ring, buffer or zonal vaccination in response to a particular, defined threat. Higher potency vaccines can be expected to induce a rapid onset of immunity within two to three days of vaccination and may also induce higher and more durable levels of antibody than standard potency vaccines with the result that they may provide protection against a wider spectrum of relevant strains following a single vaccination. It is not currently possible to define precisely a potency level above which a vaccine can be considered as a higher potency vaccine. The studies conducted to date to

determine the characteristics of higher potency vaccines have used vaccines with a potency estimated to be equal to, or greater than, the equivalent of 6PD₅₀ as measured in the Ph. Eur. potency test in cattle. However, it is not possible to be more precise as the method of estimating potency used in these studies was different to that described in the Ph. Eur. and studies have not been carried out to establish to what extent the effects observed with higher potency vaccines can also be achieved using standard potency vaccines.

'Emergency' vs. 'Routine' vaccines

This position paper does not attempt to define an 'emergency FMD vaccine' or to set limits above which a vaccine can be considered as suitable for emergency use as both standard and higher potency vaccines may be used in emergency situations depending on the numbers of animals to be vaccinated and the infection 'pressure' in the region concerned. As routine prophylactic vaccination against FMD is currently prohibited in the EU, all FMD vaccines used within the EU would be considered as 'emergency vaccines'.

Provided that an FMD vaccine has a potency at least equal to or greater than the Ph. Eur. minimum requirement, choice of potency is at the discretion of the customer and, in terms of authorisation requirements, the manufacturer must demonstrate that the vaccine has at least the potency stated on the label.

Potency testing of FMD vaccines

Methods for testing the potency of FMD vaccines are described under the section 'Efficacy'. This heading is included here under the 'Quality' section to emphasise that, in the case of FMD vaccines in particular, conventional potency testing by challenge in cattle is primarily a measure of quality control.

SAFETY

Safety studies for the purpose of authorisation

To obtain an marketing authorisation, the manufacturer should conduct safety tests as described under 'Choice of vaccine composition' in the Ph. Eur. for each species for which an indication is sought using animals of the most sensitive category. This is usually taken to mean seronegative animals of the youngest age indicated and pregnant animals. Due to the large number of antigens that might be included on an authorisation for an FMD vaccine and the essentially similar nature of these antigens after inactivation, it is considered unnecessary for a manufacturer to demonstrate the safety of each FMD antigen individually and in combination. The results of the safety test will be used to define in an authorisation the maximum number of antigens that may be incorporated into an FMD vaccine, the maximum permitted amount of each antigen, and the maximum permitted volume to be injected. The manufacturer should prepare a vaccine that contains the maximum number and the maximum permitted amount of each antigen (in terms of µg of 146S). The exact choice of antigen, in terms of serotype and strain, is at the discretion of the manufacturer but should be justified. The safety of this vaccine should be examined by conducting a safety test compliant with the requirements of the relevant general or specific Ph. Eur. monograph. Satisfactory results from this trial should be considered as sufficient evidence of the safety of the FMD vaccine concerned when formulated to contain any of the antigens permitted on the authorisation up to the maximum number, amount and volume examined in the safety test.

Safety studies for the purpose of batch release

The batch safety test should be conducted in the species most sensitive to the adverse effects of the vaccine according to the requirement of the Ph. Eur. general and specific monographs.

When a manufacturer is seeking to add a new antigen to the list of antigens included within an authorisation for an FMD vaccine it is not necessary to repeat the full safety test as described in the relevant general or specific monograph. Rather, the two animals used in the Ph. Eur. batch safety test should be carefully monitored for at least 14 days after administration of a double dose of a vaccine containing this new antigen, with or without other antigens already on the authorisation, for local and systemic adverse reactions. The reactions seen in animals vaccinated with vaccine containing the new

antigen should be compared with historic data to demonstrate that the severity and duration of the reactions observed with the new antigen are similar to that seen with vaccine formulated to contain antigens already included in the authorisation.

EFFICACY

Requirements for demonstrating immunogenicity of FMD vaccines

The requirements of Ph. Eur. monograph 0063 in terms of immunogenicity for FMD vaccines for ruminants may be demonstrated by means of the test for potency which involves challenge of groups of cattle vaccinated with varying doses of vaccine. Monograph 0063 currently requires that vaccines must have a minimum potency of 3PD₅₀ when tested in this way. Ideally, the test described under potency should be conducted at least once for each strain that is included on the authorisation. However, if justified, manufacturers may limit the demonstration of potency by challenge to a representative strain of each serotype included on the authorisation, provided that the potency of all strains included on the authorisation has been demonstrated either by challenge or by a validated alternative serological test (see below). A suitable justification might be the demonstration that the variances of the serological data for all strains examined within a particular serotype are not statistically different and that all of the data for that serotype may therefore legitimately be pooled.

Establishing alternatives to potency testing by challenge in cattle

In line with the general principles of the Ph. Eur., alternative tests may be used, provided that Competent Authorities are satisfied that the vaccine would pass the definitive Ph. Eur. test, if applied. Compliance with these requirements presents particular difficulties in the case of FMD vaccines and is the major impediment to their authorisation. Trials involving challenge with virulent FMD virus can only be conducted in specialised facilities with appropriate levels of disease security. To establish meaningful correlations between Ph. Eur. challenge tests and alternatives requires large numbers of trials for each strain of FMD examined. Restrictions of cost and accommodation usually mean that group sizes are kept to a minimum and this need is recognised in the example method included in Monograph 0063. However, as a consequence, the statistical confidence limits of each test result are wide, further limiting the ability to correlate challenge with other measures of potency.

There is considerable published data demonstrating a correlation between the presence of adequate levels of humoral antibody and protection against infection in cattle. A range of techniques have been used to measure humoral antibody, and to analyse statistically the relationship between titre and protection, but no one method has emerged as definitive.

In order for a strain to be accepted onto an authorisation by means other than by a potency test involving challenge in cattle, a manufacturer should present data, and a statistical analysis, that correlates protection with serological titre for the serotype concerned, in relation to the antigenic load.

This analysis should take into account

- the performance characteristics of the tests used to measure humoral antibody and to quantify antigenic load
- the relationship between antigenic load and serological titre induced
- the relationship between serological titre and probability of protection

By means of such an analysis, the manufacturer should justify the quantity of antigen that is blended into a vaccine in order to induce a serological response that can be correlated with at least the minimum required potency (currently 3PD₅₀). Where relevant, reference can be made to published data.

Choice of challenge strain

Conventional methods of demonstrating immunogenicity for the purposes of authorisation rely in principle on demonstrating that vaccination protects animals against virulent challenge. The degree of protection afforded by a vaccine depends both on the potency of the vaccine and on the antigenic relationship between the vaccine strain and the challenge strain. The choice of the challenge strain presents particular problems in the case of FMD virus. In general, efficacy clinical trials for registration of a vaccine should be conducted using a challenge strain that is different to the strain of

agent used as the vaccine strain (Ph. Eur. General Text 5.2.7) i.e. the challenge strain should be heterologous but antigenically related. However, due to the highly variable nature of FMD viruses, it is not possible to define what constitutes a heterologous but antigenically related strain and the more distantly related the challenge strain is from the vaccine strain the lower will be the potency when tested by challenge. For this reason, in the case of FMD vaccines, it is acceptable to use the vaccine strain itself, adapted as necessary by passage in the target species, as the challenge virus, provided that it has been shown to produce an appropriate level of clinical signs when inoculated into naïve, seronegative controls of the species for which the indication is sought. This allowance recognises that the potency test is essentially a quality control test demonstrating the capacity of the vaccine to protect in the most ideal situation (i.e. where vaccine and challenge strains are the same).

Batch potency

For batch potency testing, manufacturers should administer a suitable dose of a trial blend to no fewer than five cattle, or any other species for which immunogenicity has been shown, free of neutralising antibody to FMD virus. Antibody levels against each strain of FMD virus contained in the vaccine should be measured in samples of blood collected 21 days after immunisation. Levels should be not less than those of animals immunised with a batch that has been shown to meet the requirements of Monograph 0063 in terms of immunogenicity (see above). If satisfactory results are obtained with this trial blend, the monograph permits release of subsequent batches of FMD vaccine reconstituted from the same stock of antigen(s) without re-testing, provided that they are truly representative of the trial blend. Of prime importance in terms of being representative is the requirement that the batch to be released contains at least as much antigen, as measured by 146S content, as was contained in the trial blend. Manufacturers must therefore use a validated antigen quantification test to measure 146S antigen prior to blending. The test should be conducted on the antigen following thawing from storage immediately prior to blending and reliance cannot be placed on the 146S value obtained at the time the antigen was first frozen.

Protection against field strains

As discussed above under 'Choice of challenge strain', trials conducted by the manufacturer to demonstrate compliance with the requirements of the Ph. Eur. may be carried out using a challenge strain that is homologous to the vaccine strain. In the case of challenge tests conducted by, or on behalf of, a potential user the challenge virus will usually be a field isolate and the objective of the trial will be to establish whether or not a vaccine formulated to contain a particular antigen will provide an adequate degree of protection against the field isolate. In this situation, the apparent potency of the vaccine will depend on how antigenically similar the vaccine strain is to the field strain used as challenge. In such cases, provided that the vaccine has a PD_{50} of at least 3 against the field strain, the requirements of the Ph. Eur. are clearly met. However, a vaccine that has a potency of at least 3 PD_{50} against a homologous challenge strain but has a lower potency when a given field strain is used as the challenge, is still compliant with the Ph. Eur., even though it may not be suitable for use against that particular field strain.

Immunogenicity and batch potency in species other than cattle

For the purposes of obtaining a claim for use in a particular species, data on the immunogenicity of the FMD vaccine in that species should be demonstrated as part of the authorisation process. A Ph. Eur. monograph exists only for vaccines for ruminants and a potency test is described only for cattle. For species other than cattle, immunogenicity should be demonstrated in compliance with the requirements of the general monograph 'Vaccines for Veterinary Use'. For pigs, the test described in the OIE Manual of Standards and Diagnostic Tests, or any other suitably validated challenge test, is suitable.

Having demonstrated the immunogenicity of the vaccine in each target species, manufacturers may subsequently demonstrate the potency of batches using either the challenge test in cattle or a suitable validated alternative serological test. In general, batches shown to be potent in cattle are also likely to be potent in other species. Thus, for vaccines that are indicated both for cattle and for other species, manufacturers may demonstrate batch potency in cattle alone. Where a vaccine is not indicated for use in cattle due to particular tropism for another species (e.g. the O Taiwan strain is highly virulent for pigs but of low virulence for cattle), then immunogenicity and batch potency should be demonstrated

in the most susceptible species for which the vaccine is indicated in accordance with the general principles described in the monograph 'Vaccines for Veterinary Use'.

Indications and specific claims

An indication for use may be included on the Summary of Product Characteristics (SPC) for each target species for which immunogenicity has been demonstrated according to the requirements of the Ph. Eur. using a vaccine formulated to contain at least one of the antigens covered by the authorisation. A claim may be made for each antigen for which immunogenicity has been demonstrated and immunogenicity must be demonstrated for each antigen before it can be included on an authorisation. The claim should reflect the data presented which, in the case of a challenge test in cattle, will usually be limited to the prevention or reduction of clinical signs. Where a claim is made that a higher potency vaccine is able to induce higher levels of antibody or protection against a wider spectrum of relevant strains, this must be demonstrated.

Claims for an effect on virus excretion, or reduction of infection

It is currently unclear whether or not vaccination is able to prevent or reduce local virus excretion in animals subsequently exposed to infection. A claim for such an effect, or at most a claim for reduction of infection, would be a desirable indication for an FMD vaccine, particularly a higher potency vaccine for emergency use. Techniques for the detection and quantification of excreted virus are not standardised, but it is recognised that this virus originates from sites of replication in the upper respiratory tract. Excreted virus can be quantified either by collection of oro-pharyngeal fluid using a probang cup or by using less invasive techniques such as collecting swabs from the nose and/or mouth. Detection and quantification requires the isolation of the virus in tissue culture, detection of viral RNA by RT-PCR, or a combination of both techniques. Whilst RT-PCR techniques offer greater sensitivity, virus isolation should be considered the definitive technique, as only by isolating the virus can the replicative agent be differentiated from viral nucleic acid. In combination however, these techniques can provide unequivocal evidence of the extent to which vaccines can affect the kinetics and quantitative dynamics of virus replication and excretion, and thereby transmission. Any significant inhibitory effect, particularly during the early stages following virus exposure, may also have a bearing on persistent infection and the 'carrier' status.

For a claim to be made that a vaccine reduces local virus replication, excretion and ultimately reduces infection, a manufacturer should demonstrate that vaccination significantly reduces the relevant parameter in line with the requirements of the revised CVMP position paper on indications and specific claims for veterinary vaccines (EMA/CVMP/042/97-Rev.1).

Onset of immunity

The claim to be made on the onset of immunity will depend on what has been demonstrated in the studies. Where it is being claimed that a vaccine has a high potency and induces a rapid onset of immunity (within two to three days) this has to be demonstrated.

Duration of immunity

The duration of immunity (D.O.I.) of an FMD vaccine will depend on the formulation and the potency. As part of the authorisation procedure the manufacturer will be required to demonstrate the D.O.I. of a given vaccine by either challenge or the use of a validated alternative test, such as serology, at the end of the claimed period of protection, in compliance with CVMP/IWP/682/99 'Note for Guidance on Duration of Protection achieved by Veterinary Vaccines'. D.O.I. studies should be conducted in each species for which the vaccine is indicated or the SPC should indicate that the D.O.I. for that species is not known. Likewise, the manufacturer should demonstrate the effectiveness of the recommended booster regime in line with this guideline, usually by measuring the magnitude and kinetics of the serological response observed.

Wherever possible, manufacturers should demonstrate the D.O.I. for several different antigens as part of the authorisation procedure. In view of the similar nature of FMD antigens and the practical and animal welfare problems associated with keeping animals in isolation for extended periods of time, it is not necessary to conduct experiments to determine the D.O.I. for all strains included on an authorisation.

Appendix I: Extraneous agents of cattle required to be tested with relation to the European Union General and Species-specific Guidelines (Vol. VII of the Rules Governing Medicinal Products in the European Union)

Viral Agent	Inactivated by organic solvents**	Inactivated by Aziridines	Detectable by general tissue culture tests	Requires specific test
Adenoviruses subgroups 1 and 2	No		Yes	No
Akabane Virus	Yes		No	Yes
Aujeszky's Disease Virus	Yes		Yes	No
Bluetongue Virus and Epizootic Haemorrhagic Disease Virus	Partial	Yes	No	Yes
Bovine Coronavirus	Yes		Yes	No
Bovine Ephemeral Fever Virus	Yes		Yes	No
Bovine Herpes Viruses 1, 2, 4	Yes	Yes	Yes	No
Bovine Leukaemia Virus	Yes	Yes	No	Yes
Bovine Papillomavirus	No		#	#
Bovine Parvovirus	No	Yes*	Yes	No
Bovine Papular Stomatitis Virus	Yes		Yes	No
Bovine Respiratory Syncytial Virus	Yes		No	Yes
Bovine Rotavirus	Yes		Yes	No
Bovine Viral Diarrhoea Virus	Yes	Yes	No	Yes
Cowpox Virus	Yes		Yes	No
Foot and Mouth Disease Virus	No	Yes	Yes	Yes
Lumpy Skin Disease Virus	Yes		Yes	No
Bovine Catarrhal Fever (African Form)	Yes		Yes	No
Bovine Catarrhal Fever (European Form)	Yes		Yes	No
Parainfluenza 3 Virus	Yes		Yes	No
Rabies Virus	Yes	Yes	No	Yes
Rift Valley Fever Virus	Yes		No	Yes
Rinderpest Virus	Yes		Yes	No
Vesicular Stomatitis Virus	Yes	Yes	Yes	No

= No in vitro system allows propagation

* Porcine parvovirus is inactivated with BEI so very probable that bovine Parvovirus will also be inactivated

- ** Sources:
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 5. Inactivation of viral antigens for vaccine preparation with particular reference to the application of binary ethyleneimine. Hans. G. Bahnemann 1990 Vaccine **8**, 299-303.
 6. Inactivation of viruses in serum with binary ethyleneimine. Hans. G. Bahnemann 1976 Journal of Clinical Microbiology **3**, 2, 209-210.