Harmonising regulatory requirements for FMD vaccines within the European Union

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The recently adopted Commission Directive governing control of Foot-and-Mouth Disease (FMD) within the EU (Directive 2003/85/EC) places emphasis on vaccination as a method of control that should be considered in the first, rather than the last instance. There is therefore a greater likelihood that FMD vaccines will be used to control future incursions of the disease into the EU. In parallel, and as shown during the 2001 outbreak of FMD in the UK, the competent authorities responsible for consumer protection are paying ever increasing attention to the safety of products of animal origin. This increases pressure to ensure that vaccines used to control outbreaks of FMD are authorised to the same standards as vaccines used to control any other animal disease. This article outlines the authorisation procedures that are available for FMD vaccines within the EU, explains the measures currently in progress to make authorisation a more realistic option and describes the opportunity that currently exists to amend existing legislation to make authorisation more likely to happen in practice.

A marketing authorisation (MA) must be obtained before any veterinary medicinal product (VMP) may be placed on the market within the EU. The technical requirements that products must meet are specified in the annexes to Directive 2001/82/EC, as amended by Directive 2004/28/EC, and are described in more detail in general and specific guidelines and in the European Pharmacopoeia (Ph. Eur.). These requirements are the same whatever the route by which an MA is obtained. A national MA may be obtained by submission to the national competent authority, and subsequent approval, of a dossier demonstrating compliance with the requirements of the Directive. This MA may then be recognised by one or more other Member States of the EU through the Mutual Recognition procedure, allowing the product to be placed on the market in those member states. Recently, Council Regulation 726/2004 has been introduced which allows vaccines for diseases subject to Community control measures to be authorised through the Centralised Procedure. In this procedure, a dossier is submitted to the European Medicines Evaluation Agency and is evaluated by the Committee for Veterinary Medicinal Products (CVMP). If deemed compliant with the requirements, an authorisation is then issued by the European Commission which is valid in all Member States of the European Union.

The only exception to the requirement for an MA is an emergency provision that applies in the event of a serious disease epidemic. In such cases, Member States may permit the release of an unauthorised medicine, provided that the Commission is informed of the detailed conditions of used and provided that no authorised product is available for the disease concerned. Up until recently, this provision would have been used for the release of FMD vaccines from the strategic antigen reserves held by the EU in the EU FMD Antigen Bank. In most cases where FMD vaccines have been either formulated or actually used on a national basis, this has relied on national authorisations that had not been subject to the mutual recognition procedure. There is currently only one FMD vaccine that has been assessed as fully compliant with the requirements of Directive 2001/82, as amended, and whose authorisation has been mutually recognised.

It is important to recognise that obtaining a marketing authorisation is only the first step to release onto the market of an authorised product. Having obtained an MA, all batches of product released onto the market must pass a batch release procedure either by the manufacturer alone or through an official batch control procedure. Official batch control of immunological VMPs is not compulsory and is not harmonised throughout the EU. However, most member states apply some form of official batch control to FMD vaccines as vaccination against FMD is required under EU legislation to be under official control. The objective of official batch control is to demonstrate that the batch to be released is of the same composition and quality as the batches on which the authorisation dossier was based.

Several factors make authorisation, and subsequent release, of FMD vaccines an unattractive option for manufacturers. First, the existence of provisions allowing the release of unauthorised vaccines in the event of an emergency acts as a disincentive to manufacturers to go to the expense and inconvenience of obtaining an MA and to authorities in requiring them to have one. However, whilst an outbreak of FMD is certainly an emergency, the preparation and storage of antigens in advance of need is not. There is no reason why such antigens, and vaccines formulated from them, should not be subject to normal
regulatory requirements. Furthermore, as mentioned above, competent authorities for consumer protection are now likely to prevent products from animals which have been vaccinated with unauthorised products from entering the human food chain. Second, FMD vaccines are a ‘special case’ in regulatory terms. MAs for vaccines usually cover the release of a vaccine that contains a set number and amount of antigens in a defined formulation of excipients. In the case of FMD, an authorisation must permit the release of vaccines containing any of up to 10 or 20 different antigens (strains) alone or in combination. It is not feasible to predict, let alone test, all of these antigenic combinations, presenting particular problems in regulatory terms. In addition, in the event of incursion of a new strain of FMD into the EU, it may be necessary rapidly to adapt a field strain to become a new vaccine strain and to incorporate this into a new vaccine. Under current legislation, a new vaccine would require a new authorisation with all the consequent bureaucracy, expense and delay that this involves. Finally, once authorised, official batch control remains problematic. The definitive test for potency of FMD vaccines is currently the Ph. Eur. challenge test in cattle. The Ph. Eur. monograph on FMD vaccines for ruminants contains a specific allowance that permits release in emergency of batches formulated in exactly the same manner, and containing the same antigens, as a trial batch which has previously been shown to pass the challenge test. In practice however, manufacturers rarely wish to release exactly the same antigens in exactly the same formulation. The costs of performing challenge tests on every batch of antigen produced are prohibitive and the animal welfare implications are unacceptable. Serological alternatives to challenge therefore need to be adopted for batch release. However, the logistical and ethical difficulties of establishing statistically valid correlations between antigen load, serological titre and protection for every antigen, and every possible combination of antigens, to the standards usually required for regulatory purposes makes this an impossible solution to achieve.

In order to address the technical and scientific challenges to authorisation of FMD vaccines, the CVMP established an ad hoc group to prepare a Position Paper on requirements for FMD vaccines (EMEA/CVMP/775/02). The group comprised representatives of the CVMP Immunologicals Working Party, the European Department for the Quality of Medicines (EDQM), the Office International des Epizooties (OIE), the Research Group of the EUFMD Commission, the EMEA and the European Commission. FMD vaccine manufacturers were invited as experts and observers. At the same time, though as separate exercises, the Research Group of the EUFMD Commission was consulting with the Ph. Eur. on changes to the FMD monograph and the OIE was producing the 5th Edition of the OIE Manual. The involvement of the EDQM and the OIE in the ad hoc group ensured consistency of the CVMP requirements with those of the European Pharmacopoeia and the OIE Manual respectively.

Through the involvement of all parties, the position paper puts forward practical means whereby manufacturers can demonstrate that their products comply with the requirements of the annex to Directive 2001/82, as amended. The paper covers issues such as quality requirements for demonstrating freedom from contamination with extraneous agents; removal of non-structural proteins from concentrated antigen stock so that the vaccine will be suitable for detection of infected animals in a vaccinated population as part of a ‘vaccinate to live’ policy; how new strains might be added to an authorisation in emergency situations; how potency may be demonstrated by means other than challenge in animals, and a range of other issues of particular relevance to FMD vaccines.

The position paper describes technical solutions through which FMD vaccines can be shown to meet EU standards of quality, safety and efficacy. However, Directive 2001/82, as amended, and the associated variation regulation 1084/2003, does not currently make specific allowance for the multiplicity and interchangeability of antigens that are necessary for an FMD vaccine authorisation, nor for the rapid addition of new antigens in the event of an emergency. In the field of human disease, special provisions exist to allow human influenza vaccine strains to be updated on a regular basis in response to recommendations from WHO Reference Laboratories. A similar, but even more flexible, legislative basis is required for FMD vaccines. The annexes to Directive 2001/82, as amended, are currently being reviewed following the recent review and amendment of EU pharmaceutical legislation. This represents an ideal opportunity to create a sound legal base for the authorisation of FMD vaccines in the EU from which the technical guidance in the position paper can be operated.

In conclusion, the European Commission is urged to amend the annexes to Directive 2001/82, as amended, and Commission Regulation 1084/2003 to make specific provision for the exceptional requirements of FMD vaccines. In this way the authorisation of FMD vaccines will be promoted within the EU which will be of benefit to both animal health and consumer protection.
Conclusions
- that authorisation of FMD vaccines is desirable in the interests of animal health and consumer protection
- that sufficient general guidance on the requirements for authorisation already exists in the European Pharmacopoeia, the OIE Manual and in EU legislation and guidelines
- that the recently adopted Position Paper EMEA/CVMP/775/02 on ‘Requirements for Vaccines against Foot-and-Mouth Disease’ provides additional, specific guidance on the requirements for authorisation of FMD vaccines within the EU
- that this position paper may serve as a useful model for regulatory agencies in other regions

Recommendations
- Member Countries of the EU FMD Commission should use authorised FMD vaccines wherever possible
- Manufacturers should obtain marketing authorisations for their FMD vaccines in any country or region where they might be used
- The European Commission should amend the annexes to Directive 2001/82, as amended, and Commission Regulation 1084/2003 to make specific provision for the exceptional requirements of FMD vaccines