

Authorisation within the European Union of vaccines against antigenically variable viruses responsible for major epizootic diseases

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Summary

Antigenically variable viruses are responsible for some of the most contagious and economically important diseases that affect domestic livestock. The serious consequences of such diseases in terms of economic loss, and human and animal health, were clearly demonstrated by recent epizootics of foot and mouth disease, and outbreaks of avian influenza and bluetongue in the European Union (EU). For such diseases, government authorities need to be able to respond, if appropriate, by making use of vaccines that are suited to the epidemiological situation. The current EU regulatory framework is not well adapted for approval and maintenance of vaccines where the antigens included have to be chosen to reflect the epidemiological need. An extensive revision of the technical requirements for authorisation of veterinary medicinal products within the EU is currently underway. Additionally, a major revision of the regulations that control how such authorisations are kept up-to-date is about to start. This provides an ideal opportunity to introduce into EU legislation the concept of the 'multistrain dossier' whereby a potentially large number of approved strains may be included within a marketing authorisation and the final vaccines may be blended to include strains according to need. In addition, new strains may be added onto the marketing authorisation by means of a rapid regulatory procedure should new antigenic variants actually or potentially threaten the EU.

Keywords

Authorisation – Avian influenza – Bluetongue – European Union – Foot and mouth disease – Licensing – Vaccine.

Introduction

The recent experience of Europe with respect to foot and mouth disease (FMD), avian influenza (AI) and bluetongue (BT) has raised the issue of vaccination against these antigenically variable viruses in the mind of the general public and of those responsible for controlling these highly contagious animal diseases. This article discusses the reasons why there is a need for such vaccines to be

authorised, the factors that currently act as a disincentive to authorisation and the proposals currently under discussion aimed at promoting their authorisation.

The latter part of the 20th Century saw the introduction of regulatory systems to ensure the consistent quality of medicines in all of the major developed markets of the world, first for human medicines and subsequently for veterinary medicines. The main driver for developing these

regulatory requirements was the increasing recognition by governments and consumers of the need for medicines to be safe, of high and consistent quality, and efficacious. These requirements inevitably lead to increased costs for manufacturers both to meet the required standards and to put in place suitable systems of quality assurance. These costs can fairly readily be recouped in the case of products with a substantial and predictable market. In contrast, in the case of diseases which are exotic to the country or region concerned, or are subject to successful eradication programmes, there is little incentive for industry to invest in meeting the costs of authorising a vaccine for which the use and financial return are uncertain. On the other hand, in the case of such diseases, the consequences of not vaccinating are frequently not acceptable due to the risk of uncontrolled spread. Therefore, veterinary authorities will often seek to obtain and use an appropriate vaccine, whether or not it has met the usual regulatory requirements of the country or region concerned.

In addition to the financial disincentives, the highly complex antigenic nature of the viruses responsible for FMD, AI and BT presents particular problems in terms of authorising vaccines. Each of these viruses exist as multiple serotypes wherein the definition of a serotype is that vaccination against, or previous infection with, one serotype does not provide protection against other serotypes. Furthermore, in the case of FMD and AI, the extent of variation within each serotype is sufficiently great that not all strains within a serotype will cross-protect against each other. Each virus has its own particular mechanism by which it maintains antigenic diversity. In the case of FMD virus, this phenotypic diversity is the result of the quasispecies nature of small ribonucleic acid (RNA) viruses. The inherent imprecision of the replication mechanism of the genome results in the constant production of progeny viruses that are slightly different from their parent. Added to this, simultaneous infection with more than one strain and/or serotype of FMD virus is not uncommon and can lead to recombination. In the case of BT virus there are 24 serotypes and the virus has a segmented genome. Again, co-circulation of different serotypes is normal in endemic areas, thereby creating ideal conditions for reassortment. In the case of AI, as with other influenza viruses, antigenic drift results in the constant evolution of the antigenic nature of the prevalent strains in a population and antigen shift, as a result of reassortment, can result in the production of antigenically novel viruses with the consequent potential for pandemic spread.

It is not the intention of this paper to cover in detail the mechanisms whereby these three viruses maintain antigenic diversity. What is relevant is to emphasise the following features which these viruses have in common that present particular challenges from a regulatory perspective:

- they are antigenically complex and there is therefore a need to have in place a wide range of authorised vaccine strains
- there is a constant need to monitor the field situation to ensure that vaccine strains remain relevant and to have in place a mechanism to change strains rapidly when required
- in each case there is the potential for the rapid introduction, or development, of antigenically novel variants against which existing vaccine strains are ineffective and which therefore require the development, validation, authorisation and introduction into manufacturing of new master seed viruses in as short a space of time as possible.

Why authorise vaccines?

In view of the expense and administrative complexity that authorisation of vaccines introduces, it is important to understand why it is desirable that vaccines are authorised. As indicated in the introduction, authorisation provides assurance to the customer as to the quality, safety and efficacy of the product. In the case of vaccines used under national authority control, the customer can be said to be the national authority that purchases the vaccine from the manufacturer. National authorities see authorisation as a means of assuring the efficacy of the product without themselves having to conduct the necessary trials. In the case of all three diseases under consideration, experimental trials involving challenge with live viruses can only be conducted under highly contained conditions. The exact category of containment depends on the nature of the agent concerned but is the highest level for animals in the case of FMD virus and the highest level for both man and animals in the case of H5 highly pathogenic avian influenza viruses. Such facilities are extremely expensive to build and maintain and access to them is therefore limited on both logistical and financial grounds. For these reasons, as well as to reduce the need for testing in animals, it is highly advantageous if vaccines are authorised by an independent body based on compliance to agreed standards resulting from accumulated scientific data, thereby reducing or replacing the need for exhaustive and expensive tests in animals.

In the case of compulsory vaccination campaigns, national authorities have an obligation to provide the best possible assurance of the quality of the products used, since the stockholders have no choice as to whether or not their animals are vaccinated. In this respect, the additional assurance that is provided by independent assessment of the quality and safety of the products is extremely helpful in terms of reassurance both to the stockholders and to the

consumers of products from vaccinated animals. Recent experience with both FMD and AI has shown a reluctance on the part of some wholesalers and retailers to accept products from vaccinated animals, resulting in them opting to source produce from other, unvaccinated animals. Much of this reluctance results from ignorance of common agricultural practices and can be countered by education campaigns. However, the use of authorised vaccines provides an added level of assurance as to the safety of the vaccines themselves, and of products from animals treated with them, which is useful when seeking the support of retail organisations, stakeholder groups and independent food standards agencies.

The challenges of authorising vaccines against antigenically variable viruses

Authorisation of 'conventional' vaccines provides a high degree of regulatory certainty by permitting manufacturers to produce a product in approved premises according to Good Manufacturing Practice (GMP) and in line with the terms of a marketing authorisation (the EU term 'marketing authorisation' is used throughout this paper, but in other regulatory areas such an approval may be termed a 'product licence' or 'permit'). The marketing authorisation specifies the raw materials that are to be used, the manufacturing method to be followed and the in-process and final tests that must be performed to demonstrate the quality and consistency of the final product. A variation procedure must be approved by the licensing authority before any changes can be made to the terms of the authorisation. Thus, in the case of a vaccine, the authorisation defines a fixed formulation consisting of specified amounts, or limits, of one or more antigens derived from pre-determined master seeds blended with specified excipients and/or adjuvants.

This definition is not suited to vaccines against highly antigenically variable viruses for a number of reasons. Manufacturers will generally blend vaccines according to the epidemiological situation of the region in which they are to be used. Thus, vaccines may contain antigens derived from one or more of a wide range of master seed viruses. Under normal regulatory requirements, manufacturers would be required to demonstrate the safety and efficacy of each antigen, both individually and in combination, something which is clearly impractical when manufacturers may use any combination of up to 20 or more master seeds. Testing the safety, efficacy, onset and duration of immunity for each of 20 strains as monovalent vaccines would occupy a high containment unit for several years. Add to this trials for bi-, tri- or quadrivalent vaccines, and the myriad combinations of possible

antigens, and it is immediately apparent that a new approach is required to the authorisation of such vaccines. Under existing legislation, inclusion or substitution of a new strain into an existing vaccine would require a new authorisation which could take up to 210 days for approval. Again, a new approach is required as this is clearly unacceptable for diseases such as FMD, BT and AI where there is the potential for pandemic spread. The Committee for Medicinal Products for Veterinary Use (CVMP) of the European Medicines Agency started considering this issue following the outbreak of FMD in the United Kingdom (UK) and several other European Union (EU) Member States in 2001, ultimately resulting in the publication of the *Position Paper on Requirements for Vaccines against Foot-and-Mouth Disease* (EMEA/CVMP/775/02 – adopted June 2004) (3) and the *Guideline on Requirements for Vaccines for Use in Birds against Avian Influenza* (4).

Exceptional authorisation and use of vaccines without an authorisation

To date, the solution to these problems has been sought on a Member State level by using unauthorised vaccines or vaccines authorised under exceptional circumstances. Article 8 of Directive 2001/82/EC (as amended by Directive 2004/28/EC) (5) permits Member States to use immunological medicinal products without an authorisation 'in the event of serious epizootic disease'. Article 7 of the same Directive permits Member States to use products authorised in another Member State 'where the health situation so requires', but this is of little use where the necessary vaccines are not authorised in any Member State. Article 26 (3) of Directive 2001/82/EC for nationally authorised products, and Article 39 (7) of Regulation 726/2004 for centrally authorised products (6), provide for authorisation under exceptional circumstances for 'objective and verifiable reasons', such as the need to combat outbreaks of contagious, exotic disease and where it is not possible to conduct all of the usual tests (see below). In such circumstances some of the usual requirements for authorisation can be made into specific obligations to be carried out by the marketing authorisation holder as a condition of receiving an authorisation. These take the form of commitments to conduct studies or provide additional data to an agreed timetable after the authorisation has been issued, thereby allowing a more rapid authorisation procedure. However, such authorisations do not represent a real solution to the problem as they are reactive by nature and, due to the necessity for an annual review, burdensome in administrative terms, making them expensive both for national authorities and manufacturers.

Routes to authorisation of medicinal products within the European Union

There are two main routes to authorisation of medicinal products within the EU. In the centralised procedure, applicants apply to the European Medicines Agency (EMA) for an application to be considered by the CVMP. Following a positive opinion from the CVMP, the European Commission issues a decision granting a marketing authorisation that is valid in all 27 Member States of the EU as well as Norway, Iceland and Liechtenstein. In the national, mutual recognition or decentralised procedures, national marketing authorisations are issued in each Member State in which authorisations are sought and the Coordination Group for Mutual Recognition and Decentralised Procedures (veterinary) (CMDv) ensures that the authorisations issued are harmonised. Following the review of EU pharmaceutical legislation in 2001, several amendments were introduced to promote authorisation of vaccines against major epizootic diseases through the centralised procedure. Commission Regulation (EC) 726/2004 (6) opens up the scope of the centralised procedure to any immunological veterinary medicinal product that is used for the treatment of animal diseases that are subject to Community prophylactic measures. This therefore includes conventional, inactivated vaccines against FMD, BT and AI. In addition, it is obligatory for any vaccine produced using recombinant deoxyribonucleic acid (DNA) technology to be authorised through the centralised procedures, including recombinant or vector vaccines against these three diseases. Authorisation of vaccines to be used as part of Community campaigns through the centralised procedure has many advantages from an EU perspective in that a single authorisation permits an identical product of proven quality to be available for use in all Member States.

As mentioned above, vaccines may be authorised under exceptional circumstances through both the centralised and national procedures. An authorisation under exceptional circumstances permits Member States and the Commission to issue authorisations subject to specific obligations. This provision is necessary, for example, to exempt the manufacturer from having to conduct field trials before authorisation in view of the fact that community legislation prohibits vaccination against exotic diseases except as part of an approved vaccination campaign. Instead, the marketing authorisation holder will be required to put in place a system for enhanced pharmacovigilance (i.e. detection of side effects and adverse reactions) in the event that the product is used within the EU. In addition, the revised legislation provides for an accelerated assessment as part of the centralised

procedure of up to a maximum of 150 days for products of major importance in terms of animal health. The provisions for accelerated assessment and exceptional authorisation were both used successfully in 2006 to grant central authorisations within a total period of four months for two vaccines against AI so that authorised vaccines were available throughout the Community in time for the period of increased risk in the autumn.

The need for a specific approach to antigenically variable viruses: the concept of the 'multistrain dossier'

Whilst all of these measures are certainly helpful in promoting the authorisation and use of vaccines against diseases such as FMD, BT and AI within the EU, they are not, in themselves, likely to act as a major incentive to authorisation. The regulatory model of 'one authorisation = one fixed formulation' does not adequately take into account the complex and varied requirements for vaccines against these diseases. The technical requirements that must be met for a marketing authorisation to be initially granted are defined in Annex 1 to Directive 2001/82/EC (5). The requirements for varying a marketing authorisation once granted are defined in the variations regulations (Commission Regulations (EC) No. 1084/2003 & 1085/2003) (1, 2). Both of these sets of requirements are currently being revised by the Commission in consultation with Member States and this provides an ideal opportunity to introduce a more flexible approach to authorisation of antigenically variable viruses. This approach has been termed the 'Multistrain Dossier' concept.

The detailed guidance on how such a concept could operate in practice has yet to be elaborated. The following proposals develop the approach outlined in the CVMP *Position Paper on Requirements for Vaccines against Foot-and-Mouth Disease* and offer one potential solution. In this proposal, the authorisation for a multistrain dossier would include a number of defined, approved master seed viruses and would specify the maximum number of antigens derived from these master seeds that may be incorporated into a vaccine blend. Within these parameters, the marketing authorisation holder may then choose the actual number and type of antigens to be blended in a particular batch for a particular epidemiological situation. The amount of each antigen blended would be constrained within limits agreed with the regulator based on safety and efficacy data submitted at the time of approval of the master seed for the authorisation. This approach presupposes that all of the antigens on the authorisation are

essentially similar in all respects other than their antigenic nature. This assumption is only valid where manufacturers operate to strict standards of GMP, thereby tightly controlling all aspects of the manufacturing process such that there is a high reproducibility of production, both between different batches of the same antigen and between different antigens. This approach is only likely to be feasible for modern generation vaccines in which the antigen is well defined and, preferably, purified before blending. Provided this assumption is valid, it is then possible to extrapolate certain parameters between antigens, reducing or removing the need to repeat studies for all antigens, and all combinations of antigens, included within the authorisation. These parameters include safety, in terms of inducing adverse local and systemic reactions, and immunogenicity, in terms of onset, extent and duration of immunity. To demonstrate that extrapolation is valid, manufacturers need to supply appropriate data on batch production and testing records. These data should show the expected consistency of production and of results for in-process and final testing of stability, antigen content, batch safety and potency.

Further work is required within the regulatory community to define more precisely what data is required to accept a new master seed virus, and antigen produced from that master seed, onto the authorisation for a multistrain dossier, both at the time of authorisation and subsequently. Different requirements may apply, particularly in relation to testing for the presence of extraneous agents, depending on the urgency of the situation and therefore whether or not authorisation is sought under exceptional circumstances (see section on 'Exceptional authorisation and use of vaccines without an authorisation' above). In technical terms, to add a new master seed, the authorisation holder should demonstrate that antigen from the new seed can be produced using the method of production described in the dossier. The results of in-process and final product tests should demonstrate equivalence of the new antigen to already approved antigens. In order for the multistrain dossier approach to work in practice there needs to be a legislative mechanism that allows new strains to be added to an authorisation more quickly than is possible under the current 'line extension' procedure, which can take up to 210 days. This could either take the form of a shortened line extension procedure or, preferably, an amendment to the legislation which allows the addition of a strain onto a multistrain

dossier through a rapid variation procedure. An analogous situation already exists for human influenza vaccines whereby a change of strain to reflect the prevailing epidemiological situation is completed by means of a variation procedure within a maximum of 60 days. Furthermore, there is a legal provision for immediate acceptance of a variation in pandemic situations for influenza or other pandemic human viruses (Articles 7 and 8 of Commission Regulations (EC) No. 1084/2003 and 1085/2003) (1, 2). There is clearly value in adopting a similar approach on the veterinary side as part of the measures necessary to make the multistrain dossier approach a feasible option. In the case of vaccines for human influenza, approval of new strains is based largely on an assessment that the analytical section of the dossier demonstrates that the new antigen is of appropriate quality, together with some limited serology data. As a condition of approval, marketing authorisation holders enter into commitments to provide confirmatory evidence of efficacy in the form of data from clinical trials conducted post-approval. A similar approach would be helpful on the veterinary side in order to rapidly approve new strains in the event of epizootic situations.

Conclusion

Recent experiences with FMD, BT and AI in the EU have emphasised the need for national authorities to have access to authorised vaccines to be used as part of the control strategy for these major epizootic diseases. Amendments to the regulatory requirements would act as a significant incentive to manufacturers to authorise their vaccines. The current review of the technical requirements for obtaining and maintaining marketing authorisations within the EU presents an ideal opportunity to introduce the concept of the 'multistrain dossier'. This approach would more closely suit the particular requirements of these antigenically variable viruses and thereby promote the authorisation of high quality vaccines.

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L'agrément au sein de l'Union européenne des vaccins dirigés contre des virus épizootiques majeurs présentant une variabilité antigénique

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Résumé

Les virus présentant une variabilité antigénique sont à l'origine de maladies parmi les plus contagieuses et les plus importantes du point de vue économique qui affectent le bétail domestique. Les récentes épizooties de fièvre aphteuse et les foyers d'influenza aviaire et de fièvre catarrhale du mouton survenus dans l'Union européenne (UE) témoignent des pertes économiques que ces maladies peuvent occasionner ainsi que de leurs conséquences néfastes pour la santé humaine et animale. Face à ces maladies, les pouvoirs publics doivent être à même d'apporter une réponse appropriée, notamment en recourant à des vaccins adaptés à chaque situation épidémiologique. À l'heure actuelle, le cadre réglementaire de l'UE ne permet pas d'autoriser ni de maintenir des vaccins lorsque le choix de l'antigène doit se faire ultérieurement, en fonction des nécessités épidémiologiques. L'ensemble des exigences techniques requises pour l'autorisation de mise sur le marché des médicaments vétérinaires sont actuellement en cours de révision au sein de l'UE. En outre, les réglementations applicables à la mise à jour de ces autorisations sont également sur le point d'être examinées. La possibilité est ainsi offerte d'introduire dans la législation communautaire le concept de « demande d'autorisation multisouches », permettant aux autorisations de mise sur le marché de couvrir un nombre potentiellement important de souches approuvées de sorte que le vaccin final puisse être formulé en utilisant les souches nécessaires en fonction des besoins. De plus, grâce à une procédure réglementaire simplifiée, de nouvelles souches pourront être ajoutées aux autorisations de mise sur le marché si de nouveaux variants antigéniques viennent à menacer l'UE.

Mots-clés

Autorisation – Autorisation de mise sur le marché – Fièvre aphteuse – Fièvre catarrhale du mouton – Influenza aviaire – Union européenne – Vaccin.



Autorización de vacunas contra los virus con variaciones antigénicas responsables de las principales enfermedades epizooticas en la Unión Europea

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Resumen

Algunas de las enfermedades más contagiosas y con mayores consecuencias económicas que afectan a la ganadería de la Unión Europea (UE) pueden imputarse a virus que presentan variaciones antigénicas. Las graves pérdidas comerciales que ocasionan esas enfermedades, así como sus importantes repercusiones en la salud humana y animal, quedaron demostradas tras las epizootias de fiebre aftosa y los focos de influenza aviar y lengua azul que se produjeron en los últimos tiempos. De ser preciso, las autoridades nacionales han de poder enfrentarlas mediante medidas de inmunización adaptadas a la situación epidemiológica. El marco reglamentario en vigor en la UE no es el más conveniente para la aprobación y el mantenimiento de vacunas cuyos antígenos deben poder seleccionarse en función del pronóstico epidemiológico. En la actualidad se están examinando minuciosamente los requisitos técnicos para la autorización de medicamentos de uso veterinario en la UE. Además, está por iniciarse una profunda revisión de la reglamentación sobre la modificación de los términos de esas autorizaciones. Se trata, pues, de una ocasión que convendría aprovechar para introducir en la UE el concepto de "expedientes de multicepas", en virtud del cual se podría incluir un número potencialmente elevado de cepas aprobadas en las autorizaciones de comercialización, y las vacunas finales podrían combinarse de modo que comprendieran las cepas correspondientes a las necesidades. Además, para prever la amenaza real o potencial de nuevas variantes antigénicas en la UE, podría autorizarse la introducción de nuevas cepas en esas autorizaciones mediante un mecanismo reglamentario rápido.

Palabras clave

Autorización – Fiebre aftosa – Influenza aviar – Lengua azul – Registro – Unión Europea – Vacuna.



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