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GUIDELINE ON REQUIREMENTS FOR AN AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES FOR VACCINES FOR USE IN BIRDS AGAINST AVIAN INFLUENZA

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1. INTRODUCTION (background)

This guideline has been developed in response to the growing threat of outbreaks of avian influenza within the European Union and the lack of vaccines with Marketing Authorisations within the Community.

Avian influenza occurs worldwide and affects not only domestic poultry, but also infects a wide range of feral birds covering 88 species and 22 families, occurring most prolifically in migratory waterfowl. Type A influenza virus can also infect various species of mammals (including humans). The main reservoir of infection appears to be wild ducks, gulls, and shorebirds. Infections in poultry can be unapparent, i.e. low pathogenicity avian influenza (LPAI), or cause mild to severe respiratory disease, decreases in production, decreases in food or water intake, or cause a rapidly fatal systemic disease known as highly pathogenic avian influenza (HPAI). Important economic losses occur as a result of mortality, but also due to egg production loss, to retardation of growth, bad feed conversion and increased costs of medical treatment associated with secondary bacterial infections.

While, in the case of a lack of suitably authorised products for birds, Member States can respond to an outbreak of avian influenza with emergency vaccination by implementing Article 8 of Directive 2001/82/EC and provisionally allow the use of vaccines without an authorisation, there is an unequivocal preference to have access to authorised vaccines. In consideration of the urgent need to make suitable authorised products available, it is appropriate to make use of the provisions of Article 26 of Directive 2001/82/EC, as amended, and Article 39(7) of Regulation 726/2004 (the 'exceptional circumstances' clauses) to facilitate rapid authorisation of vaccines in advance of generation of data to meet the full requirements of Annex I to Directive 2001/82/EC as amended.

Influenza A viruses show a great antigenic diversity; there have been 16 haemagglutinin subtypes (H1 - H16) and 9 neuraminidase subtypes (N1 - N9) recognized. All these subtypes have been isolated from birds and in most possible combinations. Influenza virus identification is based on the H and N subtype present. All HPAI and all H5 and H7 viruses have been classified as Notifiable Avian Influenza (NAl) viruses by the OIE (2005).

In considering the requirements for avian influenza vaccines it is necessary to take account of the various scenarios in which they may be used:

(a) Emergency vaccination, i.e. targeted use to directly combat an outbreak of avian influenza in an EU member state or in case of a perceived immediate threat of infection occurring.

(b) Preventive vaccination, i.e. longer term vaccination to try to reduce the risk of the disease spreading into populations considered to be at risk.

(c) Routine vaccination, i.e. to maintain a high degree of immunity in birds irrespective of the perceived risk of infection.

In view of the antigenic diversity of avian influenza virus strains and the potentially high mutation rate of the virus, there may be a need to respond quickly to a rapidly evolving epidemiological situation to make vaccines available to combat the specific subtype circulating in the field. This may result in an urgent need to produce new vaccines using virus subtypes not previously authorised or to change the subtypes used in authorised vaccines at short notice.

Specific legal, regulatory and procedural provisions exist for rapid introduction of new strains into vaccines against human influenza in man. However, it must be recognised that the epidemiology of the disease and the need for disease control programmes is sufficiently different for avian influenza when compared to human influenza that there is a need to develop 'veterinary specific' measures. In the case of avian influenza, there is often a need for vaccines containing more than one avian influenza strain. Past experience with the disease in Italy and in countries outside the European Union shows

that an "old" strain might well continue to stay relevant or even return to be the most relevant strain in the future, demonstrating that the regulatory framework needs to be adapted to facilitate maintaining this strain in the authorisation, but also having the flexibility to include new strains that are epidemiologically relevant. The need for DIVA (differentiation of infection from vaccination) control strategies also supports the need for vaccines against a variety of avian influenza virus subtypes and to be able to include more than one strain in an authorisation. Additionally, there does not currently exist a well-defined procedure to provide globally approved reference strains for inclusion into all relevant marketing authorisations by a World Reference Laboratory, as is the case for human influenza. This places more emphasis on the ability of manufacturers to be able to rapidly provide and include a strain into an existing authorisation. It is, therefore, prudent to aim for a more flexible approach in order to meet the demands of Member States for suitable vaccines within appropriate timeframes.

The current regulatory framework acts as a disincentive to manufacturers of veterinary vaccines for use against diseases with a highly variable antigenic nature (in particular avian influenza, foot-and-mouth disease and bluetongue) to seek authorisation of their vaccines within the EU. The almost total lack of authorised products for such diseases, coupled with their repeated use in emergency situations in recent years, both point to the need for regulatory measures to promote their authorisation. These measures need to provide manufacturers with the flexibility to formulate vaccines using the most appropriate strains to meet a particular epidemiological situation and to be able to rapidly introduce new strains as the situation changes, while ensuring that appropriate standards of quality, safety and efficacy are maintained.

This guideline aims to provide guidance to manufacturers on the minimum data requirements for authorisation of avian influenza vaccines for emergency use under Article 26 of Directive 2001/82/EC, as amended, and Article 39(7) of Regulation 726/2004. Additional guidance on measures to facilitate the rapid inclusion of new or different virus strains in authorised vaccines and advice on requirements for vaccines intended for use in particular epidemiological situations will be the subject of a future revision.

2. SCOPE

The scope of this document is restricted to applications for an authorisation under exceptional circumstances according to Article 39 (7) of Regulation (EC) No 726/2004 for vaccines in birds against highly pathogenic avian influenza virus infections. The full requirements of Annex I to Directive 2001/82/EC apply for vaccines intended for routine and preventive vaccination.

Guidance on vaccines for use with a DIVA strategy, changing or adding new strains of avian influenza virus to an authorised vaccine and requirements for vaccine banks will be included in a future revision of this guideline.

3. LEGAL BASIS

This guideline has to be read in conjunction with the introduction and general principles (4) and Title II of the Annex I to Directive 2001/82/EC as amended.

The introduction, general principles and Title II of the Annex I to Directive 2001/82/EC as amended, lists the administrative, quality, safety and efficacy data that should be presented in support of an application. Article 39(7) of Regulation (EC) 726/2004 and Article 26(3) of Directive 2001/82/EC as amended by Directive 2004/28/EC make provision for an authorisation under exceptional circumstances where it is anticipated that additional studies may be required to meet the full requirements of Annex I Title II of Directive 2001/82/EC as amended.

It should also be noted that the use of vaccines against avian influenza within the EU is controlled under other EU legislation, notably Directive 2005/94/EC. This Directive specifies that a DIVA strategy must be used with any plan for emergency or preventive vaccination. Routine vaccination is not permitted by this legislation.

4. TYPES OF VACCINES

The following types of vaccine are examples of those that may be considered suitable for vaccination against avian influenza depending on the intended use and the epidemiological situation.

- Inactivated whole virus vaccines containing either naturally occurring strains or strains produced by reverse genetics technology to contain a particular combination of H and N antigens.

- "Subunit" vaccines containing proteins purified from avian influenza virus or produced ina biotechnology expression system.

- Live recombinant viruses (e.g. fowl pox virus, laryngotracheitis virus or Newcastle disease virus) or bacteria capable of infecting poultry species, engineered to express (an) appropriate avian influenza gene(s).

- DNA vaccines

- Virus Like Particle (VLP) vaccines

Due to their potential for genetic reassortment, as well as, in the case of H5 and H7 subtypes, a risk of spontaneous mutations leading to increased pathogenicity, avian influenza vaccines should not contain replication-competent influenza virus.

5. MINIMUM DATA REQUIREMENTS FOR AN AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES FOR VACCINES FOR USE IN BIRDS AGAINST HIGHLY PATHOGENIC AVIAN INFLUENZA VIRUS

It is anticipated that, in the event of a vaccine being required to combat an outbreak of highly pathogenic avian influenza, all of the tests required to meet the full requirements of Annex I Title II of Directive 2001/82/EC may not have been completed. The following sections outline the minimum requirements that should be met for a Marketing Authorisation to be issued in accordance with Article 39(7) of Regulation (EC) 726/2004 and Article 26(3) of Directive 2001/82/EC.

5.1 General requirements

If data meeting the full requirements of Annex I Title II of Directive 2001/82/EC are not available, the SPC should reflect any specific areas where incomplete data have been provided.

For an avian species to be included in the section "Target Species" of the SPC the outlined safety and efficacy data have to be provided. If only incomplete but relevant safety and efficacy data is available for a given species this will be stated elsewhere in the SPC.

The vaccine must only contain suitable avian influenza virus strains (one or more).

The vaccine must be manufactured under GMP conditions.

The use of conventional live vaccines is not acceptable.

5.2 Analytical (Quality) Requirements

The dossier should provide at least the following information:

- The qualitative and quantitative composition of the vaccine including the excipients and the adjuvants. The active ingredient can be live recombinant virus or bacteria, an inactivated antigen (conventional inactivated viruses or obtained by reverse genetics systems) or a subunit antigen. The origin of the vaccine strain(s) is not relevant as long as protection against the epidemiologically relevant H5 and/or H7 highly pathogenic avian influenza virus strains is induced.

- The virus strain(s) used to produce conventional inactivated vaccines should preferably be of low pathogenicity.

- A description of the manufacturing method. A quantification of the antigen content is compulsory. In principle, this should be the titre for live vaccines or the antigen content after inactivation for inactivated vaccines. However if an appropriate antigen quantification is not available, the virus titre before inactivation may be considered as long as a correlation with vaccine efficacy can be demonstrated.

- For inactivated vaccines, validation of the inactivation process should be provided. To test for complete inactivation, sequential passage through two groups of eggs will probably be sufficient. If the applicant company has experience with inactivation of other influenza strains, the evidence of which should be provided, demonstration of complete inactivation at 67% of the total time allowed will be sufficient. Otherwise a full set of data with intermediate values will be necessary

- The tests and results to demonstrate freedom from extraneous agents, which are carried out (viruses, mycoplasma) on each starting material of biological origin. With the exception of eggs, also freedom from bacteria and fungi

- The source of eggs used for the preparation of inactivated vaccines, together with information on the controls applied to minimise the risks of extraneous agents. For inactivated vaccines produced in eggs from healthy flocks it would be helpful if, coupled with this information on starting materials, information could be provided on the ability of the inactivation process applied to the antigen also to inactivate extraneous agents for which a risk has been identified. If this cannot be applied then only SPF eggs should be used for vaccine production or an extraneous agents test on the final product may be used to complete the information.

- The control of the finished product including a description of the safety and titre or potency tests (correlated with the antigen content) performed on the finished product in SPF chickens, the limits of acceptance and a declaration of the applicant that certifies that the results are within the specifications.

- The usual requirements for stability should be put in place as soon as possible for the vaccine. In the meantime supporting data of the experience with other influenza vaccines for veterinary use would be acceptable with a maximally granted shelf-life of 12 months.

- If the vaccine contains a genetically modified organism (GMO) according to Directive 2001/18/EC as amended, the full set of data with regard to Directive 2001/18 EC should be provided. It is however acceptable to fulfil part of the requirements through data which has been gained with similar GMO constructs already authorised.

5.3 Safety Requirements

The safety of the administration of an overdose to birds of the minimum age recommended for vaccination should be demonstrated in laboratory studies for all recommended target species (e.g. chickens, ducks and turkeys). For inactivated vaccines, if data are available with other vaccines of similar composition (excipients and adjuvants) in the same or a similar range of target species these could be used to fulfil the requirements. The availability of safety data for repeated administration and in other avian species would be helpful. Lack of data on repeated administration may lead to a specific obligation to be fulfilled at a later date.

Concerning safety in laying birds, whenever data related to other vaccines of similar composition are available these data could be used to fulfil the requirements with regard to reproductive performances.

If the vaccine contains a GMO according to Directive 2001/18/EC, all the requirements of Part 7 Section C Chapter 6 of Directive 2001/82/EC should be fulfilled.

All available data on safety in other species should be provided.

No field trials are required.

5.4 Efficacy Requirements

The efficacy of the vaccine should be demonstrated in laboratory conditions by a challenge model aimed to define the onset and the duration of immunity for each of the indicated target species. The challenge virus should be relevant to the current disease risk situation in the EU.

A high degree of protection against mortality and clinical signs of disease is expected.

A significant reduction of excretion and transmission of the challenge virus is a major goal. The level of reduction of excretion of challenge virus shown in laboratory studies should be sufficient to give an expectation of an acceptable level of performance in the field. If data on vaccination in the face of infection is available this should be provided in order to be reflected in the SPC if relevant.

All available data on efficacy for species other than the indicated target species should be provided, with special attention to ducks and turkeys.

No field trials are required.

Onset of immunity

The onset of immunity should be as rapid as possible to allow the use of the vaccine in emergency conditions. Any claim to be made for the onset of immunity will depend on the results of the studies performed by the Applicant. As a minimum, challenge at one time point after vaccination is required.

Duration of immunity

It is expected that the duration of immunity induced by the vaccine should cover the economic life of the target species. Any claim to be made for the duration of immunity should be demonstrated, and will depend on the results of the studies performed by the applicant. Serology may be sufficient as long as a titre that has been shown to be efficacious for the species in question is maintained for the duration claimed. Any need for revaccination should be justified and all relevant data should be provided.

5.5 Additional requirements that would be needed to meet the full requirements of the annex to Directive 2001/82/EC as amended

Marketing authorisations issued in accordance with Article 39(7) of Regulation (EC) 726/2004 and Article 26(3) of Directive 2001/82/EC must be reviewed annually.

In the event that a Marketing Authorisation is issued on the basis of the above mentioned minimum requirements but that data to meet the full requirements of the annex to Directive 2001/82/EC is lacking, then the authorisation may be subject to a requirement to provide the missing data within a defined timeframe. In general the information required will be to provide further support for the claims and warnings already included in the SPC for the indicated target species; any significant changes to the SPC will require a variation. However, the requirement for additional data needs to take into account information which may be gleaned from use of the vaccine in the field and the specific requirements may need to be reviewed depending on the use of the vaccine. The following points are relevant:

Analytical (Quality) Requirements

If validation studies for all in-process and final product tests had not been completed at the time of authorisation then appropriate data should be provided as soon as possible.

Data from routine production batches may provide assurance of the consistency of production and, for inactivated vaccines, the reliability of the inactivation process.

If adequate stability data for the vaccine was not available at the time of authorisation, stability studies should be initiated immediately and data to support the provisionally granted shelf life should be provided as soon as it is available.

Safety Requirements

If not available at the time of authorisation, GLP safety studies (single dose, overdose and, if appropriate, repeated single dose) for the vaccine should be completed for all indicated target species and using all recommended routes of administration. This should include laying birds if the vaccine is indicated for use in this category.

Information on safety of use of the vaccine in the field may be provided in place of formal field trials.

Efficacy Requirements

If not fully demonstrated at the time of authorisation, data to confirm the correlation of the potency test pass criteria with vaccine efficacy and the suitability of the approved limit should be provided.

Efficacy data (e.g. serology) obtained from field use may be used to supplement the data provided from laboratory trials, especially for species other than the target species indicated in the SPC.

The suitability of the virus type(s) included in the vaccine to provide immunity against the viruses currently circulating in the field needs to be kept continuously under review.

DEFINITIONS

The following types of **avian influenza** are defined in Annex I of Directive 2005/94/EC:

Avian influenza means an infection of poultry or other captive birds caused by any influenza A virus:

(a) of the subtypes H5 or H7; or

(b) with an intravenous pathogenicity index (IVPI) in six-week old chickens greater than 1.2;

This effectively corresponds to the OIE category of **Notifiable Avian Influenza (NAI)**;

Highly pathogenic avian influenza (HPAI) means an infection of poultry or other captive birds caused by:

(a) avian influenza viruses of the subtypes H5 or H7 with genome sequences codifying for multiple basic amino acids at the cleavage site of the haemagglutinin molecule similar to that observed for other HPAI viruses, indicating that the haemagglutinin molecule can be cleaved by a host ubiquitous protease; or

(b) avian influenza viruses with an intravenous pathogenicity index in six-week old chickens greater than 1.2;

Low pathogenic avian influenza (LPAI) means an infection of poultry or other captive birds caused by avian influenza viruses of subtypes H5 or H7 that do not come within the definition of HPAI;

Differentiating Infected from Vaccinated Animal (DIVA) strategy means a vaccination strategy which enables a differentiation to be made between vaccinated/infected and vaccinated/non-infected animals through the application of a diagnostic test designed to detect antibodies against the field virus and the use of non-vaccinated sentinel birds;