GUIDELINES FOR THE DEVELOPMENT AND REGISTRATION OF ANTICOCCIDIAL VACCINES FOR POULTRY

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Summary

Guidelines have recently been published in Avian Pathology (Chapman et al., 2005b) that are intended as an aid in the design, implementation and interpretation of laboratory, floor-pen and field studies for the assessment of the efficacy and safety of live anticoccidial vaccines for immunisation of chickens and turkeys against \textit{Eimeria} species. In addition to efficacy and safety requirements, manufacture, quality control, and licensing considerations are discussed. The guidelines do not address sub-unit vaccines, but many of the principles described will be relevant to such vaccines if they are developed in the future. Guidelines are available in some countries for avian vaccines of bacterial or viral origin but specific standards for anticoccidial vaccines in poultry have not, as far as we know, been produced. Information is provided on general requirements of registration authorities (based upon regulations applicable in the European Union and the USA) for obtaining marketing authorisations for vaccines. These guidelines may assist poultry specialists in providing specific information for administrators involved in the decision-making process leading to registration of new vaccines, and are intended to facilitate the worldwide adoption of consistent, standard procedures.

I. INTRODUCTION

It is increasingly recognized that live vaccines, based upon attenuated or non-attenuated strains of important species of \textit{Eimeria}, provide a valuable alternative to chemotherapy for the control of coccidiosis in poultry (Chapman, 2000; Chapman \textit{et al.}, 2002; Williams, 2002a,b). Anticoccidial drugs are still widely used to control coccidiosis, particularly in broiler chickens and meat type turkeys. However in some countries, such as those of the European Union, the desirability of including chemicals in animal feeds has been questioned; this has led to the withdrawal of several anticoccidial drugs from the marketplace. Other problems for prophylactic chemotherapy include reductions in the efficacy of drugs due to the acquisition of resistance by the parasites and a decline in investment in the discovery of new active agents that could serve as their eventual replacements.

The need therefore for alternative methods of coccidiosis control is urgent. For many years vaccines comprising oocysts of non-attenuated strains of pathogenic species, such as \textit{E. acervulina}, \textit{E. maxima}, and \textit{E. tenella} in chickens, and \textit{E. adenoeides}, \textit{E. gallopavonis}, and \textit{E. meleagrimitis} in turkeys have been available for use by the poultry industry. The former have principally been employed during the rearing phase of broiler breeders and to a lesser extent replacement layers, and the latter occasionally in meat type turkeys. The development of new methods of application, in particular methods that allow administration at the hatchery, has improved the practicability of vaccinating broiler chickens, and the

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development of vaccines based upon non-pathogenic (attenuated) strains of *Eimeria* has helped allay concerns of possible adverse reactions following vaccination.

The improved prospects for coccidiosis vaccines have encouraged researchers in many countries to develop vaccines for local use and in the foreseeable future several new vaccines are likely to be introduced. Companies that are experienced in the provision of high quality vaccines for the poultry industry will produce some of these vaccines but many other companies lacking such experience are also likely to be involved. It is important that all commercial vaccines, whatever their source, should be evaluated using recognized procedures and that they should be produced to the same high standards. The purpose of the guidelines is to provide a framework upon which the design, implementation and interpretation of laboratory, floor-pen and field studies for the assessment of the efficacy and safety of live anticoccidial vaccines can be based. Although the guidelines do not specifically address non-viable subunit vaccines many of the basic principles described will apply when these are developed.

II. IDEAL CHARACTERISTICS

Several ideal characteristics for any live anticoccidial vaccine can be identified. A vaccine should:
1. Induce protective immunity against economically important species of *Eimeria*.
2. Be safe for the target host, non-target animals and humans.
3. Not represent an environmental hazard.
4. Comprise parasites of normal or low virulence.
5. Comprise parasites that remain viable during storage for a reasonable period of time.
6. Protect against field strains from those geographical areas where the vaccine is used.
7. Be administered by a commercially practical method to ensure that as many birds as possible receive an immunising dose.
8. Have no adverse effects upon final performance or other production criteria.
9. Be compatible with other poultry vaccines.
10. Be free from viral, bacterial, mycoplasmal, fungal, and chemical contaminants.
11. Be cost effective compared with other methods of coccidiosis control.
12. Include drug sensitive lines that may reduce drug resistance in field populations.
13. Raise no problems with residues or impose a need for mandatory withdrawal periods.

III. EXPERIMENTAL PROCEDURES

Birds should be vaccinated under conditions that duplicate as far as possible the manner in which vaccination will be carried out in the field; subsequently they should be intentionally challenged with the parasites to see whether they have acquired protective immunity. Since immunity is species specific, the ability of a vaccine to protect against homologous parental strains of different species included in the vaccine and heterologous strains of recent field origin from different geographical locations will be necessary. Currently live oocyst vaccines are administered on a single occasion (often in the hatchery). It has been demonstrated that even for highly immunogenic species (such as *E. maxima*), reinfection, whether by vaccinal oocysts or oocysts present in the environment, is necessary for the establishment of protective immunity (Chapman et al., 2005a). Therefore, an important aspect of experimental design is that following vaccination birds must be reared in floor-pens to allow adequate exposure to oocysts; the challenge phase of experiments can be carried out in wire floored cages or pens and single-species challenges should be used (Williams and Catchpole, 2000). In the field natural challenge most frequently occurs when
birds are three to five weeks of age. Acquisition of immunity following vaccination should therefore be demonstrated by challenging birds at four weeks or earlier.

Once satisfactory results have been obtained from experimental studies then large-scale tests can be carried out in the field; this is important in order to establish that a vaccine is safe to use under field conditions. Ideally, such trials should be carried out in all geographical regions where a vaccine is intended for use.

IV. CRITERIA FOR EFFICACY

The criteria conventionally used to evaluate drug efficacy, such as weight gain, mortality, feed conversion and the presence of lesions in the intestines may similarly be used to determine the extent of immunity development following vaccination and subsequent challenge. Advantages and disadvantages of these criteria have been reviewed (Williams and Catchpole, 2000). The most useful criterion is the measurement of weight gain of vaccinated birds during the acute phase of infection following challenge with a titrated dose of oocysts that causes a decrease in weight gain without mortality. Assessment of efficacy requires comparison with the weight gain of challenged birds reared in the absence of infection (susceptible controls). In the opinion of the authors, the determination of lesion scores, using the method described by Johnson and Reid (1970), is of questionable value. Lesion scoring requires considerable expertise, is inherently subjective and, unfortunately, does not necessarily correlate with protection because lesions may be present in the gut of partially or completely immune birds even though their weight gain is not depressed.

V. REGISTRATION

In some countries registration authorities have produced guidelines for avian vaccines but specific standards for anticoccidial vaccines in poultry have not apparently so far been published. A detailed knowledge of any local requirements is essential if a product is to obtain approval. In the USA, approval to manufacture and sell veterinary anticoccidial vaccines must be sought from the USDA and requires extensive documentation to support an application for a US Veterinary Biologies Product and Establishment License. A license is also required to import vaccines from overseas. However, vaccines may be produced and used without USDA approval provided that the product was manufactured under a veterinarian-client-animal relationship, for sole use by a company in their own animals (Duquette, 2005). It is unclear whether such vaccines will be produced to the same safety and efficacy standards as those required for formal approval. In the EU procedures for registration are complex and this is dealt with in detail in the guidelines. Some of the topics covered include efficacy requirements, safety and environmental considerations, quality control in terms of purity, sterility, potency, quantification and stability etc., manufacturing practice, all to pharmacopoeial standards where specified, and last but not least necessary documentation. A monograph titled "Coccidiosis vaccine (live) for chickens" is currently under preparation and will be published in the European Pharmacopoeia.
REFERENCES