The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

CVMP/IWP/043/97-**FINAL**

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

NOTE FOR GUIDANCE

ON THE USE OF ADJUVANTED VETERINARY VACCINES

ADOPTION BY CVMP	11 November 1998
DATE FOR COMING INTO OPERATION	1 December 1998

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The intention of this note for guidance is to harmonise the European view of adjuvanted veterinary vaccines.

Introduction:

An adjuvant is considered as a substance which given in combination with an antigen increases the immune response to that antigen.
The addition of adjuvants in vaccines is often necessary when antigens characterised by a low degree of immunogenicity should be used for the production of a vaccine or to enhance the immune response to induce an early, strong and long lasting immunity.
Most adjuvanted vaccines are inactivated. Examples of the major indications for use are:

- to induce a long lasting immune response,
- to provide indirect protection of progeny via maternal antibodies from vaccinated dams
- to produce sufficient protection after a single injection.

The formulation of an adjuvanted vaccine not only depends on the presence of a given antigen and adjuvants in appropriate concentrations, but may also be influenced by the preparation methods chosen. E.g. aqueous vaccines with mineral salt hydroxides are generally very dependent on adsorption properties, and vaccines containing oils are very dependent on the emulsification procedure applied and the type of emulsion formed.

The ideal adjuvanted vaccine is safe for the treated animals, does not cause clinical or local reactions or allergic reactions and is also safe for consumers of food produced from vaccinated animals.
As such an ideal adjuvanted vaccine currently is not available some limited local and systemic reactions have to be tolerated, but without compromising consumer safety. A risk / benefit analysis has to be carried out on a case by case basis, with account being taken of animal welfare, the target species and the type of antigen. To undertake the analysis, it is recommended to follow the different steps of a risk analysis methodology. Studies on the adjuvant and the vaccine composition should be carried out during the development of the product. In order to optimise the immune response and to minimise local and systemic reactions, different ratios and quantities of the major components may need to be tested. The explanation for the choice of adjuvant and the vaccine composition, together with a summary of the supporting data, should be presented in the application dossier as requested in Part. II.A.3 - Development Pharmaceutics.

Adjuvants:

Most of the adjuvants are metallic salts (usually aluminium based) saponins and oils or oil emulsions. Other substances like bacterial derivatives, cytokines, iscoms, liposomes, and microparticles etc. may also be used now or in the future. Oil adjuvants are emulsions of compounds such as saponins, or mineral oils, containing one or more detergents, and sometimes salts.

The types of emulsion include water in oil emulsions (w/o) which cause the most intense local reactions and oil in water emulsions (o/w) which cause less intense local reactions. However, the water in oil emulsion vaccine induces a better effect on efficacy than oil in water emulsion vaccines. The last generation is the double phase adjuvants, which produce water in oil in water emulsions (w/o/w). This type of adjuvant causes significantly less local reactions.

All adjuvanted vaccines have to pass the safety and efficacy tests specified in Directive 81/852/EEC, Annex I, Title II. In addition, the MRL requirements as specified in Council Regulation (EEC) 2377/90 require consideration of the possibility of any residue remaining in the foodstuffs. Consequently, there is no risk for the health of the consumer. However, due to the various degrees of local reactions and unabsorbed adjuvants, which may persist until slaughter, the effect of the adjuvants in the tissue of the injection site has to be considered further.

Injection routes and sites of preference

Adjuvants may behave differently depending on the route and site of application. When considering the routes and sites of injection to be recommended for a product, account needs to be taken of the known local reactions from the adjuvant. The recommended routes and sites of injection should be justified in the application dossier and clearly stated in the SPC and product literature.

Test procedure for the classification of local reactions

In the current European Pharmacopoeia monographs, mainly for vaccines for pigs, as well as in the Safety data requirements of Directive 81/852/EEC as amended, it is a requirement to present precise data from detailed observations of local reactions. If appropriate the reactions should be monitored throughout safety studies, in a sufficient number of animals and until local reactions are no longer observed. At intervals, as required, in food producing species, the observations should include macroscopic post mortem examinations of the tissues surrounding the injection sites and, if necessary, microscopic examination of any lesions observed in these tissues. If justified, these observations can be restricted to the time of slaughter. These data, collected in an appropriate way are essential for assessment of the risk. Certain conditions should be applied to the studies.

- the procedure used to administer the vaccine has to be appropriate (e.g. conditions of injections and particularly use of aseptic techniques) and in compliance with the instructions in the leaflet. If these are not adequate and appropriate, secondary infections and contamination can increase the risk of complications at the injection site and create confusion with the direct effects of the adjuvant.

- a sufficient number of animals slaughtered at several stages, if necessary, during the time between the usual vaccination schedule and the mean age of slaughtering under normal rearing conditions.

- a standardised procedure should be used for examinations of local reactions:
  * to cut the muscles taking account of tissue structure,
  * to look for and measure the depth, length and width of the reactions,
  * to collect samples of lesions for histological examination.

Assessment criteria for local reactions

To classify the pathological type of lesions and of histological ones, when necessary, lesions can be placed into one of the following general categories:

- granulomas
- necrosis
- fibrosis
- abscesses (purulent granulomas)
- other inflammatory lesions

Assessment criteria for general reactions

As well as the local reactions produced by the vaccine, general reactions may be observed after vaccination. These may include pain, inappetence, fever, shivering, and depression. Careful observations should be made during safety trials and the incidence and duration of such reactions should be recorded.

Analysis of results

Several parameters have to be considered before a final decision can be taken on the effect of the product as the lesions can vary from one animal to another. Indeed, numerous factors can affect the development of the lesions: depth of the injection (length of needles), place of injection (perimysium, endomysium, and fat) lack of aseptic technique, site of injection in the animal.
In consequence, frequency, consistency, size, evolution of the lesions have to be considered before a final conclusion can be reached on the effect of the vaccine when used as recommended.

Criteria for risk/benefit analysis

Once the potential adverse effects of the adjuvant have been established, a number of factors have to be considered as part of the risk/benefit analysis of the product such as:

- the target animal species
- the category of the species
- the size of the animals

The welfare of the animal needs to be taken into account in terms of the risks from the use of the product including the reactions that may be produced and the benefits from the use of the product.
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More serious reactions are more likely to be acceptable if the vaccine prevents a serious disease and if there are no satisfactory alternative methods of treating and controlling the disease available..
Vaccines that produce abscesses are unlikely to be acceptable.
The number of doses likely to be used in the field may also be an important factor when analysing the total incidence of reactions.

A case by case assessment is clearly required. The following classifications of reactions are given as examples:

- no or very limited local and/or systemic reactions during safety testing
- small local reactions (not abscesses)
- medium local reactions (granulomas of limited extent)
- severe local reactions (granulomas extending over a large area,)
- general clinical reactions (e.g. pain, inappetence and fever)
- risk to the user, who administered the product (e.g. spray, fish dipping, injection of oil adjuvanted vaccines)

Warnings

For products where it is decided that the benefits outweigh the risks and a marketing authorisation is granted, the SPC and product literature should contain detailed warnings including of the local reactions which can be expected. These should mention the likely frequency, duration and nature of the reactions, based on the results from the studies. For vaccines for use in food producing species there should be a clear indication of the nature and duration of the reactions in the carcass, at the site of injection.

Common reactions associated with all vaccinations

In some cases, mainly when proteins from other species than the target species (such as ovalbumin) remain in the finished product, allergic reactions can be observed after the injection. The lesions are characterised by oedema, inflammatory infiltration, swelling. However, these lesions appear quickly after injection, are transient and are never observed at the time of slaughter.