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

CVMP/IWP/52/97- FINAL

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

NOTE FOR GUIDANCE:

REQUIREMENTS FOR COMBINED VETERINARY VACCINES

ADOPTED BY THE CVMP FOR RELEASE FOR CONSULTATION	16-18 MARCH 1999
DEADLINE FOR COMMENTS	19 SEPTEMBER 1999
DISCUSSION IN IWP	FEBRUARY 2000
ADOPTION BY CVMP	MARCH 2000
DATE FOR COMING INTO EFFECT	1 JANUARY 2001

Public 7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Switchboard: (+44-171) 418 8400 Fax: (+44-171) 418 8447
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

1. INTRODUCTION

1.1 Scope

There is a strong demand for harmonised regulations and a common approach to combined vaccines in the European Union. This note for guidance gives advice to manufacturers and regulatory authorities to ensure that combined vaccines as defined in this note for guidance fulfil the standards of quality, safety and efficacy. It will enable the competent authorities to arrive at their decisions by reference to uniform criteria for combined vaccines and will therefore avoid differences in evaluation.

This guideline does not address requirements for individual specific combined vaccines. For products with components which are the subject of relevant European Pharmacopoeia monographs, some specific guidance is provided in those monographs. In the case of combined vaccines, for each component that is the subject of a monograph in the European Pharmacopoeia, the provisions of that monograph apply to that component modified where necessary as indicated in the following paragraphs and as indicated in the European Pharmacopoeia monograph "Vaccines for Veterinary Use".

The rules governing veterinary medicinal products in the European Union are naturally applicable to combined vaccines to ensure their quality, safety and efficacy. The aim of this guideline is to ensure harmonisation of the requirements for the registration of combined vaccines in the European Union.

This guideline does not deal with simultaneous administration of separate vaccines.

1.2. Definitions

Combined (multivalent) vaccines are immunological products intended for

i) immunisation against different infectious diseases; or
ii) immunisation against multifactorial infectious diseases caused by different species, types or variants of pathogens
iii) combinations of (i), (ii)

In technical terms the following products are considered as combined vaccines and their use should be specifically addressed in the Summary of Product Characteristics:

a) products supplied in a single primary container;
b) products supplied in several primary packages and packed in a common secondary package with instructions for admixture before use and administration in a single site

1.3 Points to Consider for Combined Vaccine Research and Development

The development of combined vaccines is not straightforward. Each combination should be developed and studied individually in terms of quality, safety and efficacy. Initially, this includes the pharmaceutical development to establish the correct formulation, the stability of and compatibility between the individual components in the combined vaccine, including preservatives, excipients and stabilisers, inactivating agents and adjuvants.

In combined vaccines, the presence of more than one component can often cause an interaction, leading to either a diminished or an increased response to individual components, compared to when the specific component(s) is administered alone. Under justified circumstances, the diminished immune response to individual components can be acceptable.

Such interactions are often immunological in nature, but may also be caused by other factors with less direct effects on the immune system.

The potential for a vaccine combination to be more reactogenic than the individual components has to be considered. The effect of increasing toxoid load from conjugates needs to be considered. The possibility of increasing endotoxin content, particularly where components derived from Gram negative bacteria are used, also needs to be taken into account. This could be a limiting factor, for example, in combinations of inactivated bacterial vaccines containing E. coli.

The physical and chemical compatibility of these components deserves carefully drafted formulation studies preceding any clinical trials. Possible deleterious effects of vaccine components on each of the active constituents of both viral and bacterial products should be controlled. With an increasing number of components to be incorporated into a combination the problem of the volume to be administered arises. In this context, studies to concentrate the antigen amount in a given vaccine may have to be performed.

When an adjuvant is used to augment the immune response to a combined vaccine, special problems may appear. For adsorbed vaccines adjuvanticity is usually dependant on each vaccine component being firmly bound to the adjuvant, and on the presence of non-occupied sites on the adjuvant. The adsorption procedure to be used in routine manufacture must be clearly established during development since changes can result in variation in the antigen-adjuvant binding and a lack of batch to batch consistency.

2. QUALITY ASPECTS

2.1 Manufacturing and control requirements

The requirements for manufacture and control of combined vaccines are given in relevant guidelines for assuring the quality of veterinary biological products. For many combined vaccines there are already requirements available for the individual components. The methods of preparation vary according to the type of vaccine, as described in specific European Pharmacopoeia monographs, EU-legislation and manufacturers' production and control records. These methods are designed to guarantee the quality, safety and efficacy of each vaccine component, with greatest emphasis on maintaining the appropriate antigenic properties and acceptable safety as well as to ensure freedom from contamination with extraneous agents.

2.2 Formulation

Specific requirements for the ingredients such as adjuvants, antimicrobial agents, inactivating agents, antibiotics used in production, preservatives present in the finished product are specified in various guidelines for production and control of immunological veterinary medicinal products (Volume VII of the rules governing medicinal products in the EU) and in various monographs of the European Pharmacopoeia.

2.3 Stability

Stability testing of biological products requires that primary data to support a requested storage period should be based on long-term, real-time, real-condition stability studies. In the case of combined vaccines there are some special points to be considered: stability data are requested for the combined vaccine as finished product. The shelf life begins on the date of initiation of the last valid batch potency test of the first component tested and the maximum length of the storage period should always be based upon the duration of satisfactory batch potency of the least stable component and the shortest shelf life proven.

2.4 Batch testing

The following tests must be performed on the finished combined product as defined under point 1.2.

2.4.1. Safety testing

Two doses of an inactivated vaccine or ten doses of a live vaccine, *if EP monographs do not require other dosages,* are administered by a recommended route. If in cases of combined vaccines containing a live active substance the volume of 10 doses of vaccine could be unacceptably large, the number of doses of the finished product used in the test may be reduced.

If the safety test is performed on the finished combined product, no test with single components is necessary.

2.4.2 Potency testing

The aim of the release testing of a given vaccine batch is to show that this batch is consistent with and equivalent to the successive batches and to the batches that have been shown to be efficacious in clinical trials. See also position paper on batch potency testing of immunological veterinary medicinal products (CVMP/IWP/038/97-FINAL).

The testing of individual primary packages is acceptable.

3. SAFETY ASPECTS

The safety of the combined product shall be demonstrated with the vaccine containing the largest number of components. Safety tests carried out on the combined vaccines may be regarded as sufficient to demonstrate the safety of the individual components or vaccines containing a smaller number of components providing the components (antigens, composition of excipients and/or adjuvants) are identical in each case and it is only the number of active ingredients which is changed.

3.1 Laboratory trials

The safety testing requirements of Directive 81/852/EEC must be addressed during the development testing of the product. The batches used in the tests on the finished products should contain the maximum titre or potency of each component. The combined product must be shown to be safe in single, overdose and repeated dose safety studies (Annex II, III C 1,2,3) and in any studies of the effect on reproduction, immunological function and interactions (*Annex II,* III C 4,5,8). Where there is a component, which may pose a particular risk for an adverse effect on the immune system, or the reproductive performance it may be appropriate also to

conduct studies on the individual component. If the agents cannot be distinguished and re-isolated separately, each related group of live organisms may be tested separately to address the requirements for live vaccines (Annex II, III C 6).

3.2 Field trials

The test results of a combined vaccine of a larger combination may be used as results for combined vaccine of a smaller combination providing the components (antigens, composition of excipients and/or adjuvants) are identical in each case and it is only the number of active ingredients which is changed.

See also under Point 4.

4. EFFICACY ASPECTS

Combination vaccines should be studied for their appropriate efficacy parameters in the target species. Normally, the efficacy of each of the components of combined products shall be demonstrated using the combined vaccine. Test results from large combinations should be acceptable for smaller combinations of the same antigens and, under conditions specified below, vice versa, providing the components (antigens, composition of excipients and/or adjuvants) are identical in each case and it is only the number of active ingredients which is changed. Possible synergistic interactions should be evaluated.

When appropriate, dose response studies for different batches of the combined vaccine should show very similar results, indicating a consistency in the product and in the resulting immune response. Repeated challenges can be avoided by measuring parameters correlated to the immune response or which have been demonstrated to be good indicators to avoid repeated challenges.

4.1 Laboratory trials

Protection should be demonstrated by challenge with toxin or a virulent strain(s) of each organism against which the vaccine is intended to protect.

The deletion of challenges is only acceptable in rare cases and must be fully justified.

The batches used in the tests should contain the minimum titre or potency of ~~each~~ the component *to be tested in the study*.

In order to avoid repeated challenges, the results from challenge studies with monovalent vaccines or lesser combinations, which have received a marketing authorisation *in accordance with EU requirements* may be used as efficacy data for a larger combination *and vice versa*, providing certain conditions apply. Firstly, the components (antigens, composition of excipients and/or adjuvants) must be identical in each case and it is only the number of active ingredients, which is changed. There must be a marker for protection for the particular active ingredient(s), (e.g. a serological response has been shown to provide evidence of protection). Data must be provided from serological studies to show that the compounds in the larger combination provide a serological response at least equal to that stimulated by the same components in the smaller combination or superior to a threshold of acceptability. Trials must be conducted in a way that is capable of detecting any significant difference in the responses to the different products.

4.2 Field trials

The test results of a combined vaccine of a larger combination may be used as results for combined vaccine of a smaller combination *and vice versa* providing certain conditions apply. The antigen(s), which are present in the larger combination but not present in the smaller combination, should have no interference effect. There should be evidence of bio-equivalence e.g. data that the antibodies measured provide clear evidence of protection, together with data from serological studies to show that the components in the smaller combination provide a serological response which is at least equal to that stimulated by the same components in the larger combination.