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GUIDELINE ON

REQUIREMENTS FOR CONCURRENT ADMINISTRATION OF IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 47
E-mail: mail@emea.eu.int http://www.emea.eu.int

GUIDELINE ON REQUIREMENTS FOR CONCURRENT ADMINISTRATION OF IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

1. Introduction

It is recognised that in the routine use of vaccines against several different agents and/or diseases, vaccines are often administered at the same time. This practice is often necessary for sound epidemiological reasons and is beneficial to both the owner in terms of reducing costs and to the animal in terms of reducing the number of separate interventions, thus reducing stress and improving animal welfare. In Annex I of Directive 2001/82/EC a safety requirement is that any known interactions with other products shall be indicated. Under Part 8, the efficacy of each component of multivalent and combined immunological veterinary medicinal products (IVMPs) shall be demonstrated. If recommended for administration in combination with, or at the same time as another veterinary medicinal product, they shall be shown to be compatible. In Section 5.7 of the SPC guideline for immunologicals it states that safety and efficacy information should be provided to support concurrent use.

2. Scope

This guideline outlines the requirements for demonstrating compatibility for the concurrent administration (see definition under section 2.1) of two or more IVMPs. This guideline does not address the requirements for combined vaccines for which reference should be made to the CVMP Note for Guidance: "Requirements for combined veterinary vaccines". The data requirements for demonstrating compatibility for the simultaneous administration of more than one IVMP, at the same time and at the same site, in a target species are not covered by this document.

Compatibility studies should be undertaken to generate information on safety and efficacy from the concurrent use of an IVMP with one or more other IVMPs if such concurrent use is to be sought by the Applicant for inclusion in the SPC. When adequate safety and efficacy data have been generated, a compatibility statement can be included under section 5.7 of the SPC. It is expected that in most cases the studies will be undertaken as part of the safety and efficacy studies at the time of developing a new product. To provide the necessary harmonisation between the SPCs, the existing authorised products with which compatibility is to be demonstrated also need to be studied and the SPC amended accordingly to reflect compatibility with the new product.
The demonstration of compatibility between one or more preparations should not be a motivation for modifying Section 5.2 of the SPC of a product to extend the claims and indications of that product, or of the products for which compatibility has been demonstrated.

2.1 Definitions

Combined (multivalent) vaccine: A multicomponent IVMP formulated so that different antigens are administered simultaneously. The different antigenic components are intended for:

i. Immunisation against different infectious diseases; or

ii. Immunisation against multi-factorial infectious diseases caused by different species, types or variants of pathogens

iii. Combinations of i) and ii)

Simultaneous administration: For the purposes of this Guideline, simultaneous administration is defined as the administration of two or more IVMPs, at the same time and to the same site, to the target species.

Concurrent administration: The administration of two or more IVMPs at the same time, but at separate application sites in the target species. Concurrent administration can also include the

administration of two or more IVMPs to the target species at the same, or separate sites, but at different times. In the case of administration at different times, Section 5.7 of the SPC should indicate the minimum time between administrations for which data have been submitted by the applicant in compatibility studies.

Standard batch: A batch of vaccine produced according to the method described in the marketing authorisation dossier that is representative of those found in routine production and is therefore of a titre or potency intermediate between the permitted maximal and minimal values.

Separate sites: Sites sufficiently distant from each other to prevent the possibility of mixing of the products and to allow local reactions to each product to be distinguished from each other.

Separate times: Times of administration sufficiently separated to prevent mixing of the products at the site of application.

2.2 Points to consider for compatibility studies

The concurrent administration of two or more IVMPs may cause an interaction, leading to either a diminished or increased response to individual components, compared to when the IVMP is administered alone. In the case of live virus vaccines, interference between different virus strains may suppress replication of the vaccine strains resulting in a sub-optimal response.

Interference between different components can result from various immunological effects such as antigenic competition. Antigenic competition describes the phenomenon that an immune response to a particular antigen may be diminished in the presence of other antigens, compared to when the same antigen is given alone.

In the case of an adjuvanted vaccine administered concurrently with another IVMP the adjuvant may affect the response to components of the unadjuvanted product due to non-specific immunostimulation in the target species.

This guideline takes into account the fact that a considerable amount of data will have already been generated in terms of the safety and efficacy for each IVMP administered alone. The Applicant must have addressed the safety and efficacy requirements of Directive 2001/82/EC for the individual IVMPs.

In general, samples from standard batches can be used for studies to examine the safety and efficacy of IVMPs for which a compatibility statement is required. However, it is important to include a justification for the choice of batches used in the studies and the extent to which they meet the requirements. In exceptional cases additional studies with batches at maximum or minimum titre or potency may be required where data for one of the products demonstrate that one or more components exert an immunosuppressive effect likely to adversely affect the capacity of an animal to respond to other IVMPs or to render it more susceptible to adverse reactions resulting from the administration of other IVMPs.

A key issue for demonstrating the compatibility between products is the design of the studies evaluating the safety and efficacy of the concurrent use of two or more products in comparison to when the products are administered “separately”. The applicant may chose to conduct studies of safety and efficacy either under laboratory or field conditions and should justify the approach taken.

3. Quality aspects

The quality of all components of the final preparations forming the IVMPs shall comply with the specifications of the relevant general and specific monographs of the European Pharmacopoeia and Directive 2001/82/EC.

Samples used for compatibility studies should be taken from a batch or batches produced according to the manufacturing process described in the application for marketing authorisation. The product should meet the in-process and final product specifications as described in the application for marketing authorisation.

4. Safety aspects

For establishing the safety for the concurrent use of two or more IVMPs, the tests should be carried out in the most sensitive categories of each target species for which a compatibility statement is required.

4.1 Laboratory trials

The safety testing requirements of Directive 2001/82/EC must be fully addressed during the development of the individual products. If these conditions are satisfied the safety of the concurrent administration of two or more IVMPs may be demonstrated using samples taken from standard batches.

The laboratory studies for demonstrating the safety of the administration of one dose concurrently with the administration of one dose of another product shall be undertaken using a standard batch of each product for which a compatibility statement is sought**.** The dose used shall be that quantity of the product, which is recommended for use and administered to the animals of the most sensitive categories of the target species by one recommended route of administration justified by the applicant on the basis that it is most likely to result in interference.

The products shall be administered at separate sites or at separate times at the interval between vaccinations to be mentioned in the SPC. The local and systemic reactions that develop shall be monitored using the protocols followed for the establishment of the safety of a single dose of the individual product. The results obtained from the administration of the two or more products should then be compared with those obtained from the studies of the safety of the products given alone.

The safety studies submitted in support of the individual products may be used to support the safety of concurrent use. However, there may be specific situations where additional safety studies may be required e.g. the need to address the probability of recombination or genetic reassortment of related viral strains administered concurrently.

4.2 Field trials

The safety of concurrent use can be supported by adequate safety data from field trials using a standard batch of vaccine without the requirement for additional laboratory trials, provided a satisfactory justification has been provided. The local and systemic reactions should be monitored as in 4.1.

5. Efficacy

For establishing the efficacy for the concurrent use of one or more IVMPs, the tests should be carried out in the most sensitive categories of each target species for which a compatibility statement is required.

5.1 Laboratory trials

The efficacy of the concurrent administration of two or more IVMPs at separate sites may be demonstrated using samples taken from a standard batch or batches.

The dose used shall be that quantity of the product, which is recommended for use and administered to the animals by one recommended route of administration justified by the applicant on the basis that it is most likely to result in interference.

The products shall be administered at separate sites or at separate times at the interval between vaccinations to be mentioned in the SPC. The efficacy of the components in the products shall then be ascertained. The results obtained from the administration of the two or more products should then be compared with those obtained from the studies of the efficacy of the products given alone. It is expected that in the majority of cases it will be sufficient to conduct these comparisons with suitable serological studies.

In order to avoid repeated challenges, the results from challenge studies submitted in support of the individual products can be used to support the efficacy of concurrent use. Additional challenge studies may not be required where serology has previously been accepted as a correlate of protection in support of the marketing authorisation for each IVMP administered individually. Data shall be presented to demonstrate that the response of the correlate to protection is quantitatively and qualitatively the same whether the products are administered individually or concurrently. Where no such correlate exists and it is therefore necessary to conduct further challenge studies, it shall be sufficient to demonstrate efficacy of concurrent use in the most sensitive category of one of the target species.

5.2 Field trials

The efficacy of concurrent use can be supported by adequate field trials using a standard batch or batches of vaccines without the requirement of additional laboratory trials. Data shall be presented to demonstrate that the response of the correlate to protection is quantitatively and qualitatively the same whether the IVMP is administered individually or concurrently.