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## Guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products (IVMPs)

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This guideline replaces the Guideline on requirements for concurrent administration of immunological veterinary medicinal products ([EMA/CVMP/550/02](#)) and the Note for Guidance on requirements for combined veterinary vaccines ([CVMP/IWP/52/97](#)).

The effect of this guideline will be assessed by the Agency two years after it coming into effect. This report on the effects of the guideline will involve a consultation of the interested parties which provided comments on this guideline.



# Guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products (IVMPs)

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## Executive summary

This document provides guidance on the data requirements to support authorisation of combined vaccines and a claim for the use of two or more IVMPs, each with its own separate marketing authorisation, in association with one another. This term was introduced during the amendment of Title II to Annex I to Directive 2001/82/EC and there is a need to define the items covered by the term association and identify the scientific data which are necessary to justify the use of an association.

Advice is also provided on the appropriate sections of the Summary of Product Characteristics (SPC) where instructions for the use of IVMPs in association should be given.

A section is added to define terms used in the context of the use of IVMPs in association to clarify the interpretation of the different terms.

The Guideline should be read in conjunction with the Guideline on requirements for the production and control of immunological veterinary medicinal products (EMA/CVMP/IWP/206555/2010) and Directive 2010/63/EU.

## 1. Introduction (background)

Immunisation against more than one disease, pathogen and/or antigen can be provided in a number of ways as follows:

- (a) **Combined vaccine:** an IVMP intended for immunisation against more than one disease, pathogen and/or antigen which is authorised by one marketing authorisation. The combined vaccine can be supplied in a single primary container or in several primary containers, the contents of which are mixed prior to use for administration.
- (b) **Association:** The use of two or more IVMPs, each of which has its own marketing authorisation, is regarded as an association. The following associations are possible:
  - (i) mixing of two or more IVMPs prior to use for administration at one site.
  - (ii) administration of two or more IVMPs at the same time but at different administration sites
  - (iii) administration of two or more IVMPs at different times as indicated in the SPC – this covers both the administration of two or more IVMPs against different diseases/pathogens, each with its own vaccination schedule, and the administration of different IVMPs within a vaccination schedule to provide protection against the same disease/pathogen.

In the special case of intra-peritoneal injections of two or more IVMPs in fish at the same time the requirements for point (i) apply.

## 2. Scope

This document is intended to outline items to be considered and the data requirements in relation to marketing authorization applications for combined vaccines and applications where an association between two or more different IVMPs is claimed by the applicant.

This document is therefore intended to revise and compile into a single document the existing guidelines:

Guideline on requirements for concurrent administration of immunological veterinary medicinal products (EMA/CVMP/550/02) and the Note for guidance: Requirements for combined veterinary vaccines (CVMP/IWP/52/97).

The document is intended to provide guidance on the following sections of Title II of Annex I to Directive 2001/82/EC: Part 3, B, 9. and Part 4, Chapter II, A. 4., 5. and 7.

### **3. Legal aspects**

The following legal limitations apply to the types of association of IVMPs:

- an association achieved by the mixing of individual products from separate marketing authorisation holders (MAHs) cannot be authorised.
- associations of products from different MAHs (other than mixing of IVMPs) are possible providing that there is consent and agreement between the MAHs. Interactions need to be mentioned in the SPC of all IVMPs involved, which requires agreement of all MAHs involved. From a legal viewpoint such association of two or more products from different MAHs is possible but for a number of reasons seems difficult to implement. Access to data from other MAHs is required and therefore an agreement between the MAHs is necessary. In this case, the consent and agreement between MAHs should also cover responsibility for pharmacovigilance issues / reporting and information impacting variations (cf 5.1). The use of trade names of IVMPs in the product literature or a clear description of it which allows identification of the relevant product is compulsory for those IVMPs, where the safety and efficacy of the association is proven and accepted.

Changes of one product will lead to discontinuation of the association claim unless new data or justification supporting the continuation of the association is available. These changes will be subject to variation procedures.

Testing of IVMPs for animals requires safety and efficacy studies in target animals to ensure the safety and efficacy of IVMPs. Therefore, animal trials cannot be avoided. In the past demonstration of efficacy was mainly performed by challenges. However, due to the ongoing development of marker parameters for efficacy such as serological markers, the replacement of challenge trials by marker parameters is encouraged. The 3R principles (Replacement, Refinement, Reduction) as laid down in Directive 2010/63/EU are respected and supported.

## **4. Requirements for combined vaccines**

### **4.1. Data requirements**

#### **4.1.1. Quality**

The requirements for manufacture and control of combined vaccines are the same as those for an IVMP containing one active substance. They are defined in Annex I to Directive 2001/82/EC as amended and in the guidelines applicable to the IVMPs.

#### **4.1.2. Safety**

The safety requirements for combined vaccines are the same as those for IVMPs containing one active substance as defined in Annex I to Directive 2001/82/EC and in the guidelines applicable to IVMPs.

Data from laboratory and/or field safety studies carried out on a combined vaccine may be acceptable to demonstrate the safety of a vaccine containing one of the active substances or smaller combinations of the active substances providing the components (antigens, composition of excipients and/or adjuvants) are identical in each case and it is only the number of active substances which is decreased. Minor differences between the larger and smaller combined products could be accepted if suitable justification is provided.

#### **4.1.2.1. Laboratory trials**

For all laboratory safety tests, batches should contain the largest number of components which will be present in the combined vaccine, each at the highest antigen content or titre which will be present in the vaccine. For live combined vaccines where it is difficult to suspend a ten-fold maximum dose in a sufficiently small volume to be administrable to target animals of the youngest recommended age, overdose safety testing may occur at a lower than ten-fold maximum dose.

#### **4.1.2.2. Field trials**

The use of standard batches is accepted, which allows the investigation of safety and efficacy in the same field studies.

#### **4.1.3. Efficacy**

The efficacy requirements for combined vaccines are the same as those for IVMPs containing one active substance as defined in Annex I to Directive 2001/82/EC and in the guidelines applicable to IVMPs.

##### **4.1.3.1. Laboratory trials**

Protection should be demonstrated for the combined vaccine. The tests should be conducted in each target species after administration of the vaccine according to the proposed schedule of administration containing the relevant active substance(s) at the minimum antigen content / minimum titre proposed for the vaccine. Deviations from the use of the minimum antigen content / minimum titre for all of the components in a multivalent vaccine could be accepted if justified.

The onset and duration of immunity should be established for the combined vaccine. Duration of immunity may be supported by field trial data in place of laboratory studies.

If appropriate, the influence of passively acquired and maternally derived antibodies on the immunity should be adequately evaluated. The data from individual IVMPs may be suitable to address this point.

In order to avoid unnecessary challenge studies, efficacy data from a vaccine of a larger combination of active substances may be used to support the efficacy of the smaller combination provided that:

- a) the components (antigens, composition of excipients and/or adjuvants) are identical and it is only the number of active substances which is different. Minor differences between the larger and smaller combined products could be accepted if suitable justification is provided

and

- b) potential interactions of the active substances in the larger combination on the induction of protection in the vaccinated animal are taken into account.

Similarly, the results from challenge studies with a vaccine containing fewer active substances may be used to support the efficacy of the larger combination provided:

(a) the components which have already been tested for efficacy (antigens, composition of excipients and/or adjuvants) are identical and it is only the number of active substances which is different. Minor differences between the larger and smaller combined products could be accepted if suitable justification is provided.

and

(b) for one or more of the active substance(s) in the smaller combination, a threshold has been defined for a marker parameter that correlates with protection. In such cases where a challenge is not performed for the active substance(s) in the larger combined vaccine, it must be demonstrated that the results obtained for the marker parameter with the larger combination are at least equal to the threshold established for this active substance in the smaller combination. In this situation also, potential interactions of the active substances in the larger combination on the induction of protection in the vaccinated animal must be taken into account.

#### **4.1.3.2. Field trials**

Field data for a combined vaccine of a larger combination may be used to support field use of a combined vaccine of a smaller combination providing it can be demonstrated that the active substance(s), which are present in the larger combination but not present in the smaller combination, has no enhancing effects. The results obtained with an IVMP containing fewer active substances than the combined vaccine can be taken into account to demonstrate the efficacy if the conditions mentioned above (4.1.3.1.) are fulfilled.

The use of standard batches is accepted, which allows the investigation of safety and efficacy in the same field studies.

#### **4.2. SPC instructions**

The combined vaccine authorized by one marketing authorisation can be supplied in a single primary container or in several primary containers which are mixed prior to use for administration. Instructions on the mixing and the possible nature and use of devices should be provided in the SPC sections dealing with posology (amount to be administered, administration route).

## **5. Requirements for associations**

### **5.1. Items to be considered for associations**

The applicant may present a claim of association between two or more IVMPs which each have their own marketing authorisations. This means that for each individual IVMP, the quality, the safety and the efficacy were demonstrated according to the requirements of Directive 2001/82/EC. Taking this point into account, it may be acceptable to adapt the requirements of Directive 2001/82/EC to demonstrate the compatibility of the IVMPs depending on the type of association claimed.

The supporting data must take into account that the associated administration of two or more IVMPs may cause an interaction leading to either a diminished or increased immunological response to individual components, compared to when each IVMP is administered alone. For example, in the case of live virus vaccines, interference between different viral strains may suppress replication of the vaccine strains resulting in a sub-optimal response. The basis for association of IVMPs should be a demonstration of acceptable safety and absence of serious interference between the IVMPs involved. If the safety profile for the association is less favourable than that established for the separate products,

the association should be justified by an appropriate benefit-risk analysis, where the benefits of the association clearly outweigh the risks of reduced safety. In such situations, the SPCs of the separate products should be amended to reflect the safety profile due to associated use of the IVMPs. If some level of interference between the products in the association leads to a reduction of efficacy, the association of the IVMPs needs further justification on a case by case basis.

It should also be noted that changes that have an impact on the production or composition of any of the concerned IVMPs will also require re-evaluation of the compatibility of the association.

The items that should be considered for the application to support the associated use of two or more IVMPs are outlined below.

The design of the safety and efficacy studies performed to support the association of two or more IVMPs should be justified.

## **5.2. Associations due to mixing of two or more IVMPs prior to administration**

### **5.2.1. Data requirements**

#### **5.2.1.1. Quality**

The absence of negative interactions after mixing of the individual IVMPs (e.g. virucidal effect and physio-chemical interactions) should be demonstrated.

If the mixture is not to be completely used immediately then studies should be performed to support the claimed in-use shelf life for all of the components in the mixture.

#### **5.2.1.2. Safety**

The safety studies performed with the mixed IVMPs should be consistent with the requirements of Directive 2001/82/EC as amended and with the guidelines applicable to the IVMPs.

##### **5.2.1.2.1. Laboratory trials**

Special attention should be given to the following aspects:

- If justified the studies may be reduced to tests in the most sensitive category of each target species using the most sensitive route of administration.
- Unless justified, the mixed IVMPs used in the different laboratory safety studies should contain the maximum titre or antigen content.
- If different minimum ages are approved for the individual IVMPs, the safety of the association should be established for the oldest of the minimum recommended ages for the individual IVMPs. For example if vaccine A is authorised for use from 3 weeks of age and vaccine B is authorised for use from 4 weeks of age the safety of the association should be established at 4 weeks of age.
- Follow up investigations should be similar to those performed when the IVMPs are given alone.
- Comparison of the results with those obtained when the IVMPs are given alone in compliance with data already available in the marketing authorisation dossier of each IVMP should be performed.
- Results can be different but the risk/benefit balance should remain positive.

- In some cases the possibility of recombination or genetic reassortment of related live vaccine strains due to mixing of the IVMPs should be subjected to a risk analysis. Additional safety studies may be required in specific cases.

#### **5.2.1.2.2. Field trials**

For field trials, the use of standard batches is accepted, which allows the investigation of safety and efficacy in the same field studies.

The safety of associated use can be supported by adequate safety data from field trials using batches of vaccine that contain the maximum titre or antigen content without the requirement for additional laboratory trials, provided a satisfactory justification has been given and that the follow up is the same as that performed in the safety laboratory studies when the IVMPs are given alone.

#### **5.2.1.3. Efficacy**

##### **5.2.1.3.1. Laboratory trials**

In principle, the protection should be demonstrated for all components of the mixed IVMPs by challenge, according to the requirements of Annex I to Directive 2001/82/EC and with the guidelines applicable to the IVMPs. In most cases the batches being mixed should contain the minimum titre or active content and the mixture should be administered such that a single dose of each of the individual vaccines is administered to each category of each target species, by all the recommended routes of administration. However, if scientific rationale suggests that the various components might interfere with one another the relative titres or antigen content of the batches to be used might need to be considered on a case-by-case basis and appropriate justification provided for the batches selected.

Special attention should be given to the following aspects:

- Challenge against each of the active substances included in the IVMPs: If a threshold for an immune response to vaccination recognized as a correlate of protection (marker parameter) has been established for one or more of the active substances of the individual IVMPs, the challenge against these active substances can be omitted and the follow up of these marker parameters after administration of the mixed IVMPs is acceptable to support the claim for these active substances. This is only valid if it can be shown that no interactions exist between the different active substances present in the mixed IVMPs which may affect the immune response.
- If different minimum ages are approved for the individual IVMPs, the efficacy of the association should be established for the oldest of the minimum recommended ages for the individual IVMPs.
- Follow up investigations should be similar to those performed when the IVMPs are given alone.
- Comparison of the results with those obtained when the IVMPs are given alone in compliance with data already available in the MA of each IVMP should be performed.
- In the case where no immune marker parameter post-vaccination is available, challenge studies are carried out and the results must be similar and support all the efficacy claims of the individual IVMPs (some level of interference between antigens may be allowed if justified – see section 5.1).

If a follow up of marker parameters has been used, it should be demonstrated that the results obtained with the mixed IVMPs are at least equal to the threshold established for each individual IVMP.

- It should be demonstrated that the mixing of IVMPs does not negatively affect the onset and duration of immunity as established for the individual IVMPs.

#### **5.2.1.3.2. Field trials**

For field trials, the use of standard batches is accepted, which allows the investigation of safety and efficacy in the same field studies. If a marker of protection has been established, it can be followed during this trial and the results obtained with the mixed IVMPs should be at least equal to the threshold established for each individual IVMP. Field data for larger mixed combinations are sufficient to support field data for smaller mixed combinations.

#### **5.2.2. SPC instructions**

The individually authorised IVMPs are supplied in different primary containers, the content of which will require mixing prior to administration. Instructions on administration and instructions on how to mix the IVMPs should be provided in the SPC for each individual IVMP in the section dealing with posology (amounts to be administered, administration route). If any extraneous devices are needed for the mixing process they should be adequately described under the same section. Furthermore, in this section information regarding the in-use shelf life after mixing should be included.

The safety and efficacy data obtained with the mixed IVMPs should be described in the section dealing with the interactions with other medicinal products. The minimum age of vaccination for the associated use corresponding to the oldest of the minimum recommended ages for the individual IVMPs should be indicated.

The compatibility statement for mixtures should be mentioned in the section "Incompatibilities".

### **5.3. Associations due to administration of two or more IVMPs at the same time but at separate administration sites or due to administration of two or more IVMPs at separate times**

#### **5.3.1. Data requirements**

##### **5.3.1.1. Quality**

The requirements for manufacture and control of vaccines applied as association at the same time but at separate administration sites or due to administration of two or more IVMPs at separate times are the same as those for an IVMP containing one active substance. They are defined in Annex I to Directive 2001/82/EC as amended and in the guidelines applicable to the IVMPs. No additional data are required.

##### **5.3.1.2. Safety**

At least one study performed in laboratory conditions **or** in a field trial is necessary to demonstrate the safety of the association of the IVMPs. Special attention should be given to the following aspects:

- Administration of one dose of each IVMP (standard batches allowed) to the most sensitive category of each target species by one of the recommended routes (the most likely to result in interference) given either at the same time (separate sites) or at different times. In the case of different IVMPs being administered at different times, the time interval between administrations should be consistent with that mentioned in the SPC.

- If different minimum ages are approved for the individual IVMPs, the safety of the association should be established for the oldest of the minimum recommended ages for the individual IVMPs.
- Follow up investigations should be similar to those performed when the IVMPs are given alone.
- Comparison of the results with those obtained when the IVMPs are given alone in compliance with data already available in the marketing authorisation dossier of each IVMP should be performed.
- Results can be different but the risk/benefit balance should remain positive.
- In some cases the possibility of recombination or genetic re-assortment of related viral strains due to administration of the IVMPs at the same time or within a time interval which may result in recombination or genetic re-assortment should be subjected to a risk analysis. Additional safety studies may be required in specific cases.

### **5.3.1.3. Efficacy**

In principle, the protection should be demonstrated for the associated IVMPs by challenge. The batches used can be standard batches and should be administered such that a single dose of each of the individual vaccines is administered under conditions most likely to result in interference (most sensitive category of each target species, most sensitive route of administration). The IVMPs should be given either at the same time (separate sites) or at different times. In the case of IVMPs being administered at different times, the time interval between administrations should be consistent with that mentioned in the SPC.

Special attention should be given to the following aspects:

- Challenge against each of the active substances included in the IVMP: If a threshold for a immune response to vaccination recognized as a correlate of protection (marker parameter) has been established for one or more of the active substances of the individual IVMPs, the challenge against each of these active substances can be omitted and the follow up of these parameters after administration of the associated IVMPs is acceptable to support the claim for these active substances. This is only valid if it can be shown that no interactions exist between the different active substances present in the IVMPs which may affect the immune response.
- If different minimum ages are approved for the individual IVMP, the minimum age recommended for the administration of the associations should be established for the oldest of the minimum recommended ages for the individual IVMPs.
- Follow up investigations should be similar to those performed when the IVMPs are given alone.
- Comparison of the results with those obtained when the IVMPs are given alone in compliance with data already available in the MA of each IVMP should be performed.
- In the case where no immune marker parameter post-vaccination is available, challenge studies are carried out and the results must be similar and support all the efficacy claims of the individual IVMPs (some level of interference between antigens may be allowed if justified – see section 5.1). If a follow up of marker parameters has been used, it should be demonstrated that the results obtained with the associated IVMPs are at least equal to the threshold established for each individual IVMP.
- It should be demonstrated that the association of IVMPs should not negatively affect the onset and duration of immunity as established for the individual IVMPs.

- If an IVMP is developed such that it must be used in association with another IVMP in order to induce a full protection against a disease/pathogen (e.g. priming with a live vaccine followed later by a booster with an inactivated vaccine), the efficacy has to be demonstrated after the full vaccination schedule has been applied. For more details please see: Note for Guidance on duration of protection.

Where adequate justification is given, the efficacy of the association may be supported by data from a field trial(s) alone. For field trials, the use of standard batches is accepted, which allows the investigation of safety and efficacy in the same field studies. If data from a field trial(s) only are used to support the association, the following items must be considered:

- (a) a natural challenge against all of the relevant pathogens may not occur under field conditions and therefore the results of a single trial may not be sufficient to support the claims.
- (b) a marker of protection should be established which can be followed during the trial and the results obtained with the associated IVMPs should be at least equal to the threshold or limits established for each individual IVMP.

### 5.3.2. SPC instructions

The associated IVMPs are supplied in several primary containers. Instructions on administration should be provided in the section dealing with posology (amounts to be administered, administration route) of the SPC for each individual IVMP. The safety and efficacy data obtained with the IVMPs used at the same time but at separate administration sites should be described also in the section on interactions. The minimum age of vaccination for the associated use corresponding to the oldest of the minimum recommended ages for the individual IVMPs should be indicated.

When different IVMPs are associated within a vaccination schedule, the efficacy claims should be clearly indicated in the section "Indications for use" and the vaccination schedule presented in the section dealing with posology (amounts to be administered, administration route).

## Definitions

### Combined IVMP:

A combined IVMP is a medicinal product with one marketing authorisation intended for immunisation against more than one disease, pathogen and/or antigen. When the IVMP covered by the marketing authorization comprises more than one primary packaging, these should be marketed combined only and packed together unless this is not feasible, e.g. in the case of largely different vial sizes or different storage temperatures. Instructions on proper administration are provided in the section of the SPC dealing with posology (amounts to be administered, administration route).

### Associations:

The IVMPs are different veterinary medicinal products and each of them has its own marketing authorisation. The SPC of each IVMP indicates possible associated use of the products.

### Subtypes of associations:

- mixing of the IVMPs prior to use for administration at one site (formerly: simultaneous use).
- administration of the IVMPs at the same time but at separate application sites (formerly: concurrent use).

- administration of the IVMPs at separate times. The time interval should be defined and justified by the applicant (formerly: concurrent use).

The wording “concurrent use” and “simultaneous use” is mentioned here as they are mentioned in the Annex I of Directive 2001/82/EC as amended but they should not be used in the SPC as the terms are often confused and therefore the meanings may be unclear for the end user.

**Separate sites:**

Application 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. The time interval between the administrations is defined by the applicant and mentioned in the SPC.

**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.

**Marker parameter:**

A marker parameter is a specific response to a vaccination which can quantitatively be assessed and linked to efficacy. Examples of marker parameters to vaccination include:

- Immune responses to vaccination identified by serological tests that can be correlated with efficacy (immune response that is responsible for and statistically interrelated with protection).
- Marker of efficacy post challenge (e.g. reduction of excretion of the challenge organism, reduction of the load of challenge organism in blood, reduction of clinical signs).

The threshold for the marker parameter may be defined in a Ph. Eur. Monograph (e.g. immunogenicity test) and if not, by the applicant based on data from efficacy studies. Literature data can only be used to support the threshold where a justification which is acceptable to the competent authorities, is provided by the applicant,

The chosen marker parameter should offer the possibility to compare the efficacies of (1) smaller and larger combinations or (2) IVMPs administered alone and in association.