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

Draft

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

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

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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 has to 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 and/or more than one pathogen can be provided in a number of ways as follows:

(a) **Combined vaccine**: an IVMP intended for immunisation against more than one disease and/or pathogen and 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

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 (EMEA/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., 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 applicants cannot be authorised.
- associations of products from different applicants (other than mixing of IVMPs) are possible providing that there is consent and agreement between the applicants. 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 applicants 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 supporting the continuation of the association are 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. Based on the historical development of IVMPs and their proof of safety and especially efficacy was mainly performed by challenges. Due to the ongoing development of serological markers for efficacy, the replacement of challenge trials by serological marker tests 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 changed. Minor differences could be accepted if already agreed by the competent authorities.

4.1.2.1. Laboratory trials

Batches used in the laboratory safety tests 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. In justifiable cases, e.g. for live combined vaccines in one dose presentation where it is difficult to dissolve a ten-fold maximum dose in a sufficiently small volume to be administrable to target animals of the youngest recommended age, overdose safety testing of a live combined vaccine 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 of immunity and the duration of immunity should be established for each active substance of the combined vaccine. If appropriate, the influence of passively acquired and maternally derived antibodies on the immunity shall be adequately evaluated.

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

(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 could be accepted if already agreed by the competent authorities) 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 could be accepted if already agreed by the competent authorities) 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 are 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 for associations is less than the safety established for the separate products, the applicant has to justify the association by appropriate benefit-risk analysis, where the benefits of the association must clearly outweigh the 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 need to 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. 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.

Laboratory studies:

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. If different minimum ages are approved for the individual IVMP, the safety of the association should be established for the youngest age of vaccination (worst case scenario) Unless justified otherwise, the mixed IVMPs used in the different laboratory safety studies should contain the maximum titre or antigen content.

Follow up should be similar to that performed when the IVMPs are given alone.

The results should be compared with those obtained when the IVMPs are given alone (data already available in the marketing authorisation dossier of each IVMP).

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 very specific cases.

Field studies:

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 a standard batches of vaccine without the requirement for additional laboratory trials, provided a satisfactory justification has been given and that the follow up is the same as the ones performed in the safety laboratory studies when the IVMPs are given alone.

5.2.1.3. Efficacy

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 a marker parameter that is correlated with protection 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.
- Follow up similar to those performed when the IVMPs are given alone.
- Comparison of the results with those obtained when the IVMPs are given alone (data already available in the MA of each IVMP).
- Whenever challenge studies are carried out the results must be similar and support all the efficacy claims of the individual IVMPs. 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.
- If different minimum ages are approved for the individual IVMP, the efficacy of the association should be established for the youngest age of vaccination (worst case scenario) vaccination) 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.

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 should be provided in the SPCs for each individual IVMP and instructions on how to mix them should be provided 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 compatibility statement for mixture 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. 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.
- Follow up 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.
- Results can be different but the risk/benefit balance should remain positive.

In some cases the possibility of recombination or genetic reassortment 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 reassortment should be subjected to a risk analysis. Additional safety studies may be required in very specific cases.

If different minimum ages are approved for the individual IVMP, the safety of the association should be established for the youngest age of vaccination (worst case scenario) vaccination)

5.3.1.2. 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 marker parameter that is correlated with protection has been established for one or more of the actives of the individual IVMPs, the challenge against each of these actives 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.
- Follow up should be similar to that 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.

- Results must be similar and support all the efficacy claims of the individual IVMPs. 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 one 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. 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 the 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.

If different minimum ages are approved for the individual IVMP, the minimum age recommended for the administration of the associations should be the worst case scenario (minimum age of vaccination) For field trials, the use of standard batches is accepted, which allows the investigation of safety and efficacy in the same field studies.

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 SPCs/ for each individual IVMP and points relevant to administration of the association should be included in the section on interactions. 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.

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 one medicinal product intended for immunisation against more than one disease and/or pathogen with one marketing authorisation. 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 impossible, 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 be 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.