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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 current version of the Guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products (IVMPs) (EMA/CVMP/IWP/594618/2010). The guideline was revised in order to adapt legal references to the current legislation and reflect the experience that was gained with the guideline since it is in force. In addition, new approaches in vaccine development and alternative approaches to assess the absence of immunological interference in the associated use of vaccines are considered in the revision.

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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

Regulation (EU) 2019/6 of the European Parliament and of the Council requests that for combined and multivalent IVMPs as well as for the use of two or more IVMPs, each with its own separate marketing authorisation, in association with one another, safety and efficacy shall be demonstrated. This document provides guidance on the data requirements to support authorisation of combined vaccines and of a compatibility statement with other IVMPs. Advice is given on the scientific data which are necessary to justify the use of an association, considering the principles of 3Rs as defined in Directive 2010/63/EU wherever possible.

Advice is also provided on the appropriate sections of the product information, 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, where relevant, the Guideline on data requirements for vaccine platform technology master files (vPTMF) (EMA/CVMP/IWP/286631/2021).

1. Introduction (background)

Immunisation against more than one disease, pathogen and/or antigen as well as against multiple strains of a causative agent of the same disease can be provided in a number of ways, such as:

(a) **Combined vaccine**: an IVMP intended for immunisation against more than one disease, pathogen and/or antigen as well as against multiple strains of a causative agent of the same disease, 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. Vector vaccines inducing claimed immunity against more than one antigen are regarded as combined vaccines in this context.

(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 product information – 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.

Definitions

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 product information.

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.

Indicator of protection:

For an indicator to be acceptable as a correlate of efficacy for a specific type of vaccine(s), it shall be demonstrated that a sufficient correlation exists between the indicator measured and the claimed protection in the target species. An indicator of protection should be shown to play a substantial role in the immune response, relevant for protection of the target species against the disease concerned. Reference to literature may be used to support the role of the indicator in the protection but is not sufficient to define the level necessary to guarantee efficacy of vaccination. It must be demonstrated that the level of response obtained for the indicator in the efficacy studies is equal to the one observed in vaccinated animals at the time of challenge in pre-clinical trials and for which protection was demonstrated. For example, if the serological follow-up of neutralising antibodies has been shown to be an indicator of protection, it should be demonstrated that the minimum protective level of neutralising antibodies associated with protection at the time of challenge is obtained in the other efficacy studies.

Indicator of lack of immunological interference

An indicator of lack of immunological interference is a parameter, for which correlation to protection was not established, but which is considered suitable to indicate that the immune response against each of the vaccines that are used in association is still acceptable. Most commonly, serological markers are used as indicator of lack of immunological interference.

2. Scope

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

The document is intended to provide guidance on section IIIb of Annex II to Regulation (EU) 2019/6.

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. The associated use and possible

interactions then need to be mentioned in the product information of all IVMPs involved. The consent and agreement between MAHs on the associated use of different products should also cover responsibility for pharmacovigilance issues / reporting and information impacting variations. The use of trade names of IVMPs in the product information or a clear description, which allows identification of the relevant products, is compulsory for those IVMPs, where the safety and efficacy of the association is proven and accepted.

If any of the products concerned undergoes a change that requires new safety and efficacy studies, it must be justified that this change does not have a negative effect on the associated use claim. In case the change implemented by a variation requires adaptation of the product information in regard to an associated use claim, this will be subject to a variation procedure for the concerned product(s).

The safety and efficacy of the associated IVMPs have to be demonstrated in target animals. In the past, efficacy of the associated use was mainly demonstrated in challenge studies. However, the use of suitable indicators of protection or indicators of lack of immunological interference (e.g. serological markers) to replace challenge studies is encouraged. If appropriate, the indicator used to support the efficacy of the associated use shall be mentioned in the product information.

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 Regulation (EU) 2019/6 and in the guidelines applicable to IVMPs.

4.1.2. Safety

The safety requirements for combined vaccines are the same as those for IVMPs containing one active substance as defined Regulation (EU) 2019/6 and in the guidelines applicable to IVMPs.

Data from pre-clinical and/or clinical 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. For marketing application dossiers for new vaccines using an approved vPTMF(s), a possible reduction in safety requirements is mentioned in guideline EMA/CVMP/IWP/286631/2021.

4.1.2.1. Pre-clinical studies

For all pre-clinical safety studies, 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.

4.1.2.2. Clinical trials

The requirements for clinical safety trials of combined vaccines are basically the same as those for an IVMP containing one active substance. The use of standard batches is accepted, which allows the investigation of safety and efficacy in the same clinical studies. For vector vaccines using an approved vPTMFs, clinical safety studies may be omitted, if satisfactorily justified according to guideline EMA/CVMP/IWP/286631/2021.

4.1.3. Efficacy

The efficacy requirements for combined vaccines are the same as those for IVMPs containing one active substance as defined in Regulation (EU) 2019/6 and in the guidelines applicable to IVMPs. For new vaccines using an approved vPTMF(s), a reduction in efficacy requirements can be justified according to guideline EMA/CVMP/IWP/286631/2021.

4.1.3.1. Pre-clinical studies

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.

Onset and duration of immunity should be established for the combined vaccine. Duration of immunity may be supported by clinical trial data in place of pre-clinical 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 enhancing interactions of the active substances in the larger combination on the induction of protection in the vaccinated animal are considered and discussed.

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 to the antigens included in the combined vaccine and it is only the number of active substances which differs between smaller and larger combinations. Minor differences in composition 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 an indicator of protection 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 indicator of protection parameter with the larger combination are at least equal to the threshold established for this active substance in the smaller combination.

4.1.3.2. Clinical trials

Clinical 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 justified, that the active substances, 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 considered to demonstrate the efficacy if the conditions mentioned above (4.1.3.1.) are fulfilled.

The use of standard batches is accepted, to allow the investigation of safety and efficacy in the same clinical studies.

4.2. Product information instructions

If the combined vaccine is supplied 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 sections of the product information dealing with posology.

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. IVMPs for associated use can be vaccines with one or more antigens or vector vaccines for which the quality, the safety and the efficacy were demonstrated according to the requirements of Regulation (EU) 2019/6. Regarding this point, it may be acceptable to adapt the requirements of Regulation (EU) 2019/6 to demonstrate the compatibility of the IVMPs depending on the type of association claimed.

The supporting data must consider 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. The basis for association of IVMPs should be a demonstration of an acceptable safety and efficacy profile of the associated use. 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 product information documents 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. 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 after preparation, studies should be performed to support the shortest claimed in-use shelf life of all of the components in the mixture, which will then be applicable for the mixed use.

5.2.1.2. Safety

The safety studies performed with the mixed IVMPs should be consistent with the requirements of Regulation (EU) 2019/6 and with the guidelines applicable to IVMPs.

5.2.1.2.1. Pre-clinical 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.
- Unless justified otherwise, the mixed IVMPs used in the different pre-clinical 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 of 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, and the associated use can take place at 4 weeks of age at the earliest.
- Follow up investigations in associated use studies should be similar to those performed when the IVMPs are given individually and if applicable in compliance with Ph. Eur. requirements.
- Comparison of the results of associated use studies with data obtained when the IVMPs are given individually and which are included in the corresponding marketing authorisation (MA) dossier of each IVMP should be performed.
- Results may differ, 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. This has to be decided on a case-by-case basis.

5.2.1.2.2. Clinical studies

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

The safety of associated (mixed) use can be supported by adequate safety data from clinical trials alone, using batches of vaccine that contain the maximum titre or antigen content, provided a satisfactory justification has been given and that the follow up is the same as in the safety pre-clinical

studies when the IVMPs are given individually. On the other hand, the omission of clinical safety trials can be justified when pre-clinical data demonstrate an acceptable safety profile for mixed use.

5.2.1.3. Efficacy

5.2.1.3.1. Pre-clinical studies

The lack of interference between vaccines in case of associated use should be demonstrated for all components of the mixed IVMPs by challenge studies or alternative approaches, such as the use of indicators of protection or any other relevant immune response parameter, according to the requirements of Regulation (EU) 2019/6 and in compliance with the guidelines applicable to IVMPs. In most cases the mixed vaccines should contain the minimum titre or active content (deviations should be justified). The mixture should be administered in a way 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 or the worst-case route (if known for the individual IVMPs). 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 recognised as an indicator of protection 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 indicator of protection parameters after administration of the mixed IVMPs is acceptable to support the claim for these active substances. If different minimum ages are approved for the individual IVMPs, the efficacy of the entire mixture should be established for the oldest of the minimum recommended ages for the individual IVMPs, as from this age on the associated use is applicable.
- Follow-up investigations should be similar to those performed when the IVMPs are applied individually and if applicable, in compliance with Ph. Eur. requirements.
- The results shall be compared and be in compliance with data obtained when the IVMPs are applied individually and that are already available in the MA of each IVMP.
- Where no indicator of protection parameter post-vaccination is available, challenge studies may have to be carried out, and the results must be similar to the results of single-use studies and support all the efficacy claims of the individual IVMPs (some level of interference between antigens may be allowed if satisfactorily justified – see section 5.1).
- If a follow-up of indicator of protection 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 neither a challenge is performed, nor an indicator of protection is established, the lack of interference may be shown by follow-up of relevant immune response parameters that should not be affected by the associated use compared to the immune responses observed after administration of the individual IVMPs.
- It should be demonstrated that the mixing of IVMPs does not negatively affect the onset of immunity as established for the individual IVMPs. However, a rationale should be provided why the duration of immunity will not be affected for each of the mixed vaccines.
- In case of associated use of combined vaccines, including vector vaccines, a larger combination of active substances/ construct with more inserts may be used to support the compatibility of a smaller combination, if the vaccines basically differ only in the number of antigenic components.

5.2.1.3.2. Clinical trials

For clinical trials, the use of standard batches is accepted to allow the investigation of safety and efficacy in the same field studies. If an indicator of protection parameter or a parameter showing absence of immunological interference 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. Clinical data of larger mixed combinations can be used for smaller mixed combinations. The omission of clinical trials can be justified when pre-clinical data demonstrate an acceptable efficacy profile for mixed use.

5.2.2. Product information instructions

The individually authorised IVMPs are supplied in different primary containers, the content of which will require mixing prior to administration. Instructions on mixing and administration should be provided in the product information for each individual IVMP in the section dealing with posology. Any device required for the mixing of the vaccines should be adequately described. Information on the in-use shelf life after mixing should also be included.

Safety and efficacy data obtained with the mixed IVMPs should be described in the section dealing with interactions with other medicinal products. If regarded necessary, it shall be stated in the product information when compatibility claims are based on indicators of protection or on absence of interference on immune responses. The minimum age for associated use should correspond to the oldest of the minimum recommended ages of the individual IVMPs and should be clearly indicated.

The compatibility statement for mixtures should be mentioned in the section on 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 Regulation (EU) 2019/6 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 clinical 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 one most likely to result in interference) applied either at the same time (separate sites) or at different time points. In case of different IVMPs are administered at different time points, the time interval between administrations should be consistent with what is claimed and mentioned in the product information.

- 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, which will then be overall applicable for the associated use of the concerned vaccines.
- Follow-up investigations in associated-use studies should be similar to those performed when the IVMPs are applied individually and if applicable in compliance with Ph. Eur. requirements.
- Comparison of the results of associated-use studies with those obtained when the IVMPs are applied individually and which are already available in the MA dossier of each IVMP should be performed.
- Results may 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 may result in recombination or genetic re-assortment should be subject to a risk analysis. Additional safety studies and/or additional warnings/recommendations in the SPC may be required in specific cases. This is decided on a case-by-case basis.

5.3.1.3. Efficacy

The lack of interference between vaccines used in association should be demonstrated for all components of the IVMPs by challenge studies or alternative approaches, such as the use of indicators of protection or any other relevant immune response parameter, according to the requirements of Regulation (EU) 2019/6. 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 time points according to the proposed association claim. In case IVMPs are administered at different timepoints, the time interval between administrations should be consistent with what is claimed and mentioned in the product information.

Special attention should be given to the following aspects:

- Challenge against each of the active substances included in the IVMP: If a threshold for an immune response to vaccination recognised as an indicator of protection 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.
- If different minimum ages for vaccination are approved for the individual IVMPs, the oldest of the minimum recommended ages established for the individual IVMPs should be recommended for the associated use.
- Follow-up investigations should be similar to those performed when the IVMPs are applied individually and if applicable, in compliance with Ph. Eur. requirements.
- Comparison of the results of associated-use studies with those obtained when the IVMPs are applied individually that are available in corresponding dossiers should be performed.
- In case where no immune indicator of protection parameter post-vaccination is available, challenge studies may have to be carried out, and the results must be similar to the results of single-use studies and support all the efficacy claims of the individual IVMPs (some level of

interference between antigens may be allowed if satisfactorily justified – see section 5.1). If a follow-up of indicator of protection 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.

- If neither a challenge is performed, nor an indicator of protection is established, the lack of interference may be shown by follow-up of relevant immune response parameters that should not be affected by the associated use compared to the immune responses observed after administration of the individual IVMPs.
- It should be demonstrated that the association of IVMPs should not negatively affect the onset of immunity as established for the individual IVMPs. However, a rationale should be provided as to why the duration of immunity will not be affected for each of the vaccines given in associated use.
- If an IVMP is developed in a way 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.
- Where adequate justification is provided, the efficacy of the association may be solely supported by data from either pre-clinical studies or clinical trials. For clinical trials, the use of standard batches is accepted to allow the investigation of safety and efficacy in the same clinical studies. If data from a clinical 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) an indicator of protection parameter 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.

  (c) If neither a challenge is performed, nor an indicator of protection is established, the lack of interference may be shown by follow-up of relevant immune response parameters that should not be affected by the associated use compared to the immune responses observed after administration of the individual IVMPs.

In case of associated use with combined- or vector vaccines, a larger combination of active substances/ construct with more inserts may be used to support the compatibility of the smaller combination, if the vaccines basically only differ in the number of antigenic components.

5.3.2. Product information instructions

The associated IVMPs are supplied in several primary containers. Instructions on administration should be provided in the section dealing with posology of the product information for each individual IVMP. Safety and efficacy data obtained with the IVMPs used at the same time but at separate administration sites should be described in the section on interactions. If regarded necessary, it shall be stated in the product information when compatibility claims are based on indicators of protection or on absence of interference on immune responses. The minimum age of vaccination for the associated use should correspond to the oldest of the minimum recommended ages established for the individual IVMPs and be clearly indicated.

If different IVMPs are associated within a vaccination schedule, the efficacy claims should be clearly indicated in the section dealing with indications and the vaccination schedule presented in the section dealing with posology.