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Guideline on the use of adjuvanted veterinary vaccines

Draft

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The guideline aims to replace the Note for guidance on the use of adjuvanted veterinary vaccines (EMA/CVMP/IWP/043/97) adopted by the Committee in November 1996.

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 use of adjuvanted veterinary vaccines

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Executive summary

The main aim of the guideline is to outline the information which should be included for the adjuvant in the marketing authorisation application (MAA) of an immunological veterinary medicinal product (IVMP).

This guideline replaces the 'Note for Guidance on the use of adjuvanted veterinary vaccines'.

The guideline discusses the important aspects to consider for the adjuvant in an IVMP and provides guidance on the information on the adjuvant which should be included in Parts 2, 3 and 4 of the MAA. The details on the adjuvant which should be referred to in the SPC of the IVMP is also addressed in this guideline.

1. Introduction (background)

An adjuvant is a substance which, when included in a vaccine, modulates the immune response to the vaccine active substance(s) to enhance the clinical effectiveness of the vaccine. For example an adjuvant may increase the immunogenicity of the active substance(s) thereby reducing the amount of active substance(s) required for successful immunisation or may modify the induced protective immune response e.g. extending its duration, thereby removing the requirement for booster vaccinations or extending the interval between vaccinations. Adjuvants can also be used to optimise a desired immune response e.g. with respect to immunoglobulin classes and/or induction of cytotoxic or helper T lymphocyte responses.

Some of the mechanisms by which adjuvants may exert their activities include:

- protection of the vaccine active substance(s) from biodegradation thus increasing their retention at the site of vaccine administration for prolonged stimulation of the immune system
- activation of the innate immune system by delivering signals to inflammatory cells, thus facilitating uptake of the vaccine active substance(s) and processing by antigen presenting cells (APCs)
- distribution of the processed active substance(s) and enhancement of their presentation by APCs to the adaptive immune system to stimulate humoral and / or cell mediated immunity

Mineral based adjuvants (e.g. aluminium hydroxide, aluminium or calcium phosphate salts) are delivery / depot type adjuvants which retain the vaccine active substance(s) at the injection site facilitating presentation of the active substance(s) to the immune system. Mineral based adjuvants may also function as inflammatory signals at the site of injection which leads to the synthesis of pro-inflammatory cytokines and stimulation of innate immunity (1).

Oil-in-water and water-in-oil-in-water emulsions are examples of other depot type adjuvants that as well as delivering the active substance(s) to the immune system may also promote slow release of the active substance(s) by protecting them from biodegradation at and rapid elimination from the site of administration (2).

Saponin based adjuvant systems, e.g. Quil A, extracted from the *Quillaja saponaria* bark and its purified derivative QS-21 may facilitate transfer of the active substance by APCs from the site of injection to the regional lymph nodes to stimulate the adaptive immune system, resulting in activation of T-helper cells, generation of high-affinity antibodies from B cells and sometimes also T cytotoxic cells (3).

Immunomodulatory substances inducing specific modulating effects on selected targets of the immune system may also be used as adjuvants or as a component of an adjuvant. For example, synthetic oligonucleotides containing CpG motifs of bacterial DNA and purified fractions of lipopolysaccharide such as monophosphoryl lipid A (MPLA) are toll like receptor (TLR) agonists used as adjuvants. Activation of TLRs stimulate synthesis and release of pro-inflammatory cytokines / chemokines and type I interferons that directly trigger innate immune responses (4 - 6).

As adjuvant activity is a result of multiple factors and active substances vary in their physical, biological and immunogenic properties, the modulation of the immune response obtained with one active substance – adjuvant combination cannot as a rule be extrapolated to other active substance – adjuvant combinations.

Adjuvants should be chosen based on the type of immune response desired and should be formulated with the active substance(s) of the vaccine in such a way that the optimal type of immune response with minimal adverse effects is obtained.

There are some specific references in Annex 1, Title II to Directive 2001/82/EC (Requirements for immunological veterinary medicinal products (IVMP)) that detail where information on adjuvants should be provided e.g. Part 2.A. 'qualitative composition of the adjuvants' and Part 2.E.4 'identification and assay of adjuvant'. In addition, there is a general requirement that the safety profile of the active substance - adjuvant combination should be examined and any user, consumer or environmental safety issues be identified and addressed. Further, the efficacy of the combination should be demonstrated in each category of the target species as applicable.

2. Scope

For the purposes of this guideline an adjuvant is defined as a substance or a composition of substances which when used in combination with a specific active substance(s), potentiates the immune response and / or modulates it towards a desired immune response which cannot be achieved by administration of the active substance(s) alone in order to enhance the efficacy of the vaccine.

The intention of this guideline is to outline the type of data to be submitted in the application dossier in relation to the adjuvant(s) used in an IVMP to meet the requirements of Annex 1, Title II to Directive 2001/82/EC.

In the case of an adjuvant in an IVMP classified as MUMS, the reduced data requirements listed in EMA/CVMP/IWP/123243/2006-Rev.3 "Guideline on data requirements for immunological veterinary medicinal products intended for minor use or minor species (MUMS)/limited market" are applicable, where relevant.

3. Legal basis and relevant guidelines

This Guideline should be read in conjunction with the introduction and general principles of Title II to Annex I to Directive 2001/82/EC and all other relevant EU guidelines as well as relevant European pharmacopoeial monographs. These include, but are not limited to:

- Guideline on requirements for the production and control of immunological veterinary medicinal products (EMA/CVMP/IWP/206555/2010-Rev.1).
- Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin.

- Substances considered as not falling within the scope of Regulation (EC) No. 470/2009 with regards to residues of veterinary medicinal products in foodstuffs of animal origin (EMA/CVMP/519714/2009).
- Guideline on user safety for immunological veterinary medicinal products (EMEA/CVMP/IWP/54533/2006).
- Ph. Eur. 0062: 'Vaccines for veterinary use'.

4. Data requirements

4.1. Data requirements for Part 2, Quality (Chemical, Pharmaceutical and Biological/Microbiological information)

Qualitative and quantitative composition

In the description of the qualitative and quantitative composition of the vaccine, a clear distinction should be made between adjuvant components and other vaccine excipients.

Where there is more than one adjuvant and / or the adjuvant(s) consists of a number of components, the qualitative and quantitative composition and function (e.g. immune modulator, stabiliser, emulsifier) of all of the components of the adjuvant(s) should be stated in the table of qualitative and quantitative particulars in the dossier. Where the adjuvant is commercially available and a trade name is used the trade name should be identified as this is useful for pharmacovigilance purposes. However the trade name alone may not provide sufficient detail of the nature and composition of the adjuvant(s) therefore as much detail as possible on the components should be given in the dossier using the chemical / biological names where appropriate.

It is recognised that the details of the adjuvant composition may be considered commercially sensitive information. In such cases, provided that the adjuvant composition is defined in the dossier and where adequate justification is given, it may not be necessary to disclose the exact composition of the adjuvant in publically available documents (e.g. product information) and the European Public Assessment Report (EPAR)). However Volume 6C of the Notice to Applicants "SPC- Immunologicals", states 'the qualitative and quantitative composition of the adjuvant(s) should be stated where knowledge of this is essential for the safe administration of the medicinal product'. On this basis, the SPC section 2 should include quantitative details of the component(s) responsible for the immune modulatory effect. For those components not listed quantitatively in the SPC section 2, it should be explained why they are not considered to have an immune modulatory effect. A qualitative listing of all the components of the adjuvant should be given in SPC Section 6.1.

Product development

The chosen active substance(s) – adjuvant(s) combination at the quantitative composition proposed for the IVMP should be described and justified.

The mechanism of action of the chosen adjuvant(s) in combination with the active substance(s) in the proposed target species when the vaccine is given according to the proposed administration route(s) should be described in as much detail as possible. The type of information to be discussed includes:

- the manner in which the adjuvant(s) (and the individual components of the adjuvant) exerts its effects e.g. presentation of the active substance(s) to the immune system; targeting of the active substance(s) to specific cells; optimising the uptake of the active substance(s); protection of the active substance(s) from degradation and elimination to permit prolonged stimulation of the immune system;

- the type of immune response triggered by the active substance(s) – adjuvant(s) combination e.g. innate / adaptive immune response; humoral / cell-mediated response, T-helper response (Th1/Th2); and,
- the type of interaction between the adjuvant(s) and the active substances(s) (e.g. adsorption; ionic interactions; encapsulation) and the importance of the interaction to stimulate an immune response in the target species.

An overview of the safety profile of the active substance(s) - adjuvant combination should be provided giving due consideration to the mechanism(s) of action of the adjuvant and its components. As well as its effect on the immunogenicity of the active substance(s), the potential for any allergic or auto-immune responses that may be induced by the adjuvant or as a result of its interactions with the vaccine components including impurities should be considered. Where risks are identified, appropriate risk mitigation measures should be proposed. To support the choice of the adjuvant, its mechanism of action and expected safety profile of the proposed active substance(s) - adjuvant combination reference can be made to other vaccines marketed in the EU containing the same or similar adjuvant(s) and / or adjuvant components and to published literature.

Reference to and reliance on publically available information may not be adequate where the concentration of the adjuvant and / or active substance(s) is higher than in IVMPs authorised to date (e.g. increase in active substance concentration which could also result in an increased level of impurities in the vaccine) or where a combination of adjuvants are used in a new IVMP being submitted for authorisation where the combined adjuvant system has not yet received an authorisation in the EU. In such cases, additional proprietary data should be provided.

The information referred to above in conjunction with data from the safety studies on the IVMP in Part 3 of the dossier must support a positive benefit-risk profile for the active substance(s) – adjuvant(s) combination proposed for the IVMP.

A reference to the vaccine efficacy studies in Part 4 of the dossier can be made to support the efficacy profile of the chosen active substance – adjuvant combination in all categories of the proposed target species. Data from preliminary / pilot studies generated during vaccine development can be provided in the ‘Product Development’ section of the dossier.

Description of the manufacturing method

The steps involved in the manufacturing processes of the adjuvant(s) and blending of the adjuvant(s) and the vaccine active substance(s) and excipients should be described in detail.

Critical steps / parameters in the production and mixing processes considered important for association of the active substance(s) and the adjuvant(s) and / or adjuvant component(s) should be outlined. For example, for oil based adjuvants, the description of the emulsification process should include details such as the process scale and size and type of equipment used, temperature, duration, speed, pH adjustment and any critical parameters for successful formation of the emulsion. Details of the sterilisation conditions for the adjuvant(s) / adjuvant components should also be provided for each stage of production to the final product.

The proposed manufacturing process for the adjuvant(s) and for blending with the vaccine active substances(s) and excipients should have been applied in the manufacture of the vaccine batches supporting the batch to batch consistency of the production process (see section on ‘batch to batch consistency’ below) and in the manufacture of the batches used in the safety and efficacy studies in Parts 3 and 4 of the dossier respectively. Any deviations should be described and justified.

Production & Control of starting materials

Details of the source of the adjuvant(s) and each of the adjuvant components where relevant (e.g. of chemical or biological origin) should be given.

The routine tests and specifications applied to the adjuvant(s) and / or the adjuvant components should be described. Ideally these should include tests to check for the correct physical, biochemical, biological or adsorptive properties of the adjuvant(s). The tests chosen should be justified and a sample certificate of analysis should be provided.

Depending on the nature of the adjuvant and its components, the requirements of some European Pharmacopoeia monographs and CVMP guidelines may also be applicable (in addition to those listed under Section 3 above). While not an exhaustive list, examples of relevant documents that may apply include:

- Ph. Eur. 2034 “Substances for pharmaceutical use”
- Ph. Eur. 5.2.5 ”Management of extraneous agents in IVMPs”
- Ph. Eur. 0784 ”Recombinant DNA technology, products of”
- Ph. Eur. 1483 ”Products with risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products”

Control tests during the manufacturing process and Control tests on the finished product

A description of the tests applied as controls for the critical steps/parameters in the production of the adjuvant(s) and /or mixing with the active substance(s) and excipients to guarantee the consistency and integrity of the adjuvant in routine vaccine batches should be given. The limits for each test should be defined with appropriate justification and data on the validation of each test should be provided.

The tests may include in-process tests on the adjuvant and any of the adjuvant components during manufacture of the adjuvant system and / or during formulation of the vaccine in addition to tests on the finished vaccine.

The choice of tests used should be justified. Items to consider include (but are not limited to):

- Suitability of the test(s) to measure the qualitative and quantitative composition of the components of the adjuvant that have an immune-stimulating effect
- Suitability of the test(s) to measure the physico-chemical and biological characteristics of the adjuvant and /or active-adjuvant combination to ensure the consistency and integrity of the combination in routine vaccine batches.

An *in-vitro* test should preferentially be used to test for the adjuvant and / or its components in the finished vaccine batch. In line with the requirements of Directive 2010/63/EU and the EMA Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012), the continued use of *in-vivo* potency tests simply on the basis that they support the performance of the active ingredient–adjuvant combination is no longer considered an adequate justification for not developing alternative *in-vitro* tests for IVMPs.

It is recognised that there may be situations where it is difficult to quantify the adjuvant and / or its components in the vaccine formulation due to interference from other components of the vaccine formulation. In exceptional circumstances, and only when a suitable justification can be given, alternative approaches may be acceptable e.g. quantification of the adjuvant(s) and / or its components in the solution prior to addition to the active substance(s) during blending to confirm that the correct amount of adjuvant is added to the vaccine blend. However, when tests for the quantitative

composition of the adjuvant are not done on the finished vaccine, some level of testing should be performed to support the suitability of the interaction between the active substance(s) and the adjuvant in the finished vaccine (e.g. particle size distribution, viscosity, conductivity, etc.), where possible.

The in-process and final product tests proposed for routine vaccine batches should have been performed on the consistency batches (refer to section on 'batch to batch consistency' below) and on the batches used in the safety and efficacy studies discussed in Parts 3 and 4 of the dossier respectively to ensure consistency between routine and clinical trial batches. Any deviations should be justified.

Batch to batch consistency

Data from three consecutive vaccine batches which are representative of the proposed manufacturing process should be provided. In the case of emulsion adjuvants in particular where the consistency of the emulsion is dependent on the size of mixing vessels and equipment, the scale of the process used in the production of the consistency batches should be representative of that proposed for routine batches. Batch protocols for the consistency batches should be provided and should include results of the in-process and finished product tests proposed for the adjuvant(s) and / or its components.

Stability

During the stability studies on the vaccine, appropriate qualitative and / or quantitative tests, preferably *in-vitro* tests should be performed to support the integrity of the adjuvant and its components throughout the shelf life of the vaccine. For example, tests for phase separation during storage are important for vaccines containing emulsion adjuvants.

4.2. Data requirements for Part 3 Safety

Data should be submitted in accordance with the requirements of 'Part 3: Safety tests' of Annex 1, Title II to Directive 2001/82/EC and according to the requirements of Ph. Eur. 5.2.6 'Evaluation of safety of veterinary vaccines and immunosera'.

Ph. Eur. 5.2.6 requires the animals used in the safety studies to be examined 'for signs of local and systemic reactions' when the vaccine is given by 'each of the recommended routes of administration'. The adverse reactions monitored in the vaccine safety studies should take into consideration the mechanism of action of the adjuvant and its interaction with other vaccine components as discussed in the Product Development section of the dossier.

For food producing species the safety of residues of the adjuvant(s) and / or its components for human consumption of the foodstuffs must be addressed and an appropriate withdrawal period for the product proposed if required.

Applicants should ensure that the maximum residue limit (MRL) status of each of their adjuvants is addressed in advance of submitting the marketing authorisation dossier.

If the adjuvant has a 'no MRL required' classification according to Regulation (EC) No 37/2010 or is included in the list of substances considered as not falling within the scope of Regulation (EC) No. 470/2009 (that is, the 'out-of-scope' list), no additional information is required and the absence of a risk for the consumer can be accepted provided that the conditions of use (if any) mentioned in the Regulation or the 'out-of-scope' list are met.

If the adjuvant does not have an MRL classification and is not included in the out of scope list, then the MRL status of the adjuvant must be addressed. This can be achieved by means of an MRL application

or, in case of absence of pharmacological activity, by a request to include the adjuvant in the 'out of scope' list.

An excipient (including an adjuvant) that is not listed in either Table 1 of Commission Regulation (EC) 37/2010 or the out-of-scope list, can only be used in a veterinary medicinal product intended for food producing species if it is concluded that the substance cannot be expected to show pharmacodynamic activity at the dose at which it is/will be administered to the target animal. In exceptional cases, particularly when considering branded excipients (including an adjuvant) made up of numerous ingredients, evidence for absence of pharmacodynamic activity and justification for classifying the excipient as falling outside the scope of the MRL regulation may be considered within the scope of the marketing authorisation application. However, applicants are advised to discuss the acceptability of this approach with the relevant competent authority before submission of the application.

When assessing the user safety of the active substance(s) – adjuvant combination in accordance with the requirements of Part 3.B 7 of Title II annex 1 of 2001/82/EC, potential hazards associated with the adjuvant should be identified in the application dossier. For example parenterally administered vaccines containing mineral oil adjuvants represent a particular risk to the user if self-injected. Refer to EMEA/CVMP/IWP/54533/2006: 'Guideline on user safety for immunological veterinary medicinal products' for more details.

Similarly when assessing the environmental risk of the active substance(s) - adjuvant combination in accordance with the requirements of Part 3.D of Title II annex 1 of 2001/82/EC consideration should be given to the potential harmful effects to the environment due to the adjuvant or its components and identify any precautionary measures to reduce such risks.

4.3. Data requirements for Part 4 Efficacy

Data should be submitted in accordance with the requirements of 'Part 4: Efficacy tests' of Annex 1, Title II to Directive 2001/82/EC and according to the requirements of Ph. Eur. 5.2.7 'Evaluation of efficacy of veterinary vaccines and immunosera'.

5. Definitions

The following definitions apply to terms used in this guideline:

Active substance: The active substance is the component of the IVMP to which an immune response is desired. IVMPs may contain one or more active substances.

Adjuvant: Substance or a composition of substances which when used in an IVMP potentiates the immune response to the active substance(s) of the vaccine and / or modulates it towards a desired immune response which cannot be achieved by administration of the active substance(s) alone.

Immunomodulator: A substance inducing a specific modulating effect(s) on a selected cell target(s) to generate optimal adaptive immune responses(s). Substances containing sequences found in the pathogen associated molecular patterns (PAMPs) of bacterial and viral DNA, dsRNA, lipopolysaccharide (LPS), bacterial flagellin are examples of immunomodulators used as adjuvants in vaccine formulations.

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