

INCLUSION OF ANTIMICROBIAL PRESERVATIVES IN IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

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Additional Notes	This guidance describes the principles that should be considered before including antimicrobial preservatives in immunological veterinary products. It should be read in conjunction with the European Pharmacopoeia monograph "Efficacy of Antimicrobial Preservation".

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1. INTRODUCTION

In this document, "preservative" means an antimicrobial preservative added to a medicinal product to prevent spoilage or adverse effects arising from microbial contamination during use. Trace quantities of antibodies or preservatives left over from production are not included.

The European Pharmacopoeia has adopted a monograph entitled "Efficacy of Antimicrobial Preservation". The monograph lists a range of designated bacterial and fungal species to be used in the efficacy test, these being supplemented, where appropriate, by other strains or species which may represent likely contaminants to the preparation. The test protocols appear to be designed for simplicity and reproducibility of results, rather than for reflecting the complexity of naturally-occurring contamination situations. Thus, the range of designated bacterial test species excludes anaerobes and spore-formers, for example, and the prescribed strains do not have the penicillin and mercury resistance of those sometimes encountered in veterinary practice. The viral aspects of preservation have not been addressed in the pharmacopoeia.

Antimicrobial preservatives must not be used as a substitute for Good Manufacturing Practice (GMP). Nevertheless, preservatives have traditionally been included routinely by manufacturers in immunological products. However, in view of the desirability of excluding potentially toxic excipients from medicinal products where possible, and the emphasis on formulation, manufacturing methodology and GMP as a means of achieving an acceptable product, preservatives would not seem to have a role in single dose sterile products.

In general, veterinary medicinal products are likely to be at risk from microbiological contamination because of the circumstances under which they may be administered, and those containing substantial amounts of biological macromolecules are particularly difficult to preserve. For these reasons, and because of their limited stability following reconstitution and/or removal from refrigeration, multidose parenteral immunological veterinary medicinal products should be allocated an in use shelf life of no longer than one working day (8 to 10 hours). The exact proposed in use shelf life must be accompanied by a justification based on appropriate stability and microbial safety data.

2. GUIDING PRINCIPLES

- 2.1 Immunological veterinary medicinal products in single dose containers shall normally not contain a preservative. Exceptions (e.g. where there is a practice of simultaneous manufacture and marketing of both single dose and multidose presentations) shall be justified.
- 2.2 Multidose liquid preparations (including emulsions) must be protected from harmful microbial contamination after first opening or broaching the container. One approach may be the addition of a preservative at a concentration which has been demonstrated during product development studies to be effective in combating the growth of

representative bacterial and fungal species. Any proposal to market a product in a multidose container must be accompanied by a justification (including supporting data) vis-à-vis the non-inclusion or inclusion, as appropriate, of a preservative. This justification may refer, for example, to the delivery system(s) to be used to administer the product.

- 2.3 In selecting a preservative system the applicant should consider
- the effectiveness against potential microbial contaminants;
 - possible interaction with the formulation or container (for example, thiomersal is ineffective in sera, and can bind to SH groups and polymeric material);
 - the potential pharmacological and toxicological effects on the target animal species, at the dose rates appropriate to the veterinary medicinal product;
 - any maximum residue limits which have been fixed for the preservative substance(s), if appropriate;
 - possible effects on testing of the immunological veterinary medicinal product, for example tests on cell cultures or mammalian species.
- 2.4 Preservatives may not be added to products that are to be freeze-dried, though they may be present in the diluent for reconstitution when the innocuousness of the preservative for the lyophilised product has been proven, and where allowed by points 2.1 – 2.3 above.
- 2.5 The test procedures and microorganisms employed for demonstrating preservative efficacy should be as outlined in the Ph. Eur. Monograph “Efficacy of Antimicrobial Preservation”. The range of microorganisms chosen for the testing should reflect the potential risk. As the Ph. Eur. allows some flexibility in the experimental conditions and range of microorganisms, the materials and methods for testing should be described in appropriate detail by the applicant, who must in particular validate the method to “ensure that any residual antimicrobial activity of the product is eliminated by dilution, filtration or by the use of a specific inactivator” in the recovery operation.
- The ideal acceptance criteria are the Ph. Eur. A-criteria. However, in view of the short in use shelf-lives appropriate to multidose parenteral immunological veterinary medicinal products (in general no longer than one working day or 8 to 10 hours as discussed in the introduction), the sampling of inoculated products in the case of preservative efficacy studies on these products should be at a minimum of three intervals covering the period of the proposed in use shelf life. For example, samples might be collected at 0, 3, 6, and possibly 9 hours, to demonstrate the kinetics of the preservative efficacy. For bacteria, at least two log reductions in viable count should ideally be achieved by six hours, with no increase thereafter, and for fungi, no increase in viable count should occur over the sampling period.
- 2.6 The applicant is encouraged to provide additional evidence of microbiological safety, for example by a multiple vial broaching test.
- 2.7 The finished product specification for any preparation containing a preservative should include tests for both the identity and concentration of the preservative. In the case of concentration, a specification within $\pm 15\%$ of label claim at time of release is acceptable.
- 2.8 For products containing a preservative, the maintenance of preservative efficacy throughout the period of the shelf life should be demonstrated during the stability studies.

- 2.9 The name and concentration of any preservative present in an immunological veterinary medicinal product should be stated on the labelling. Or, where this is not possible, in the package insert text. In the case of multidose parenteral products, the in use shelf life, justified on the basis of development testing as outlined in 2.5 above, should also be stated on the labelling, for example as "any product still extant more than x hours after first broaching the seal should be discarded". The product literature for multidose parenteral products should in addition include directions to use only sterile needles and syringes for administration and to avoid the introduction of contamination during use.