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Guideline on data requirements to support in-use stability claims for veterinary vaccines

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Executive summary

This guideline outlines the data that should be provided in support of in-use shelf-life claims for veterinary vaccines. The aim of this guideline is to provide a framework which will enable applicants to maintain a consistent approach when generating data in support of allocating an appropriate in-use shelf-life to a veterinary vaccine, based on existing regulatory requirements

1. Introduction

Veterinary vaccines may be marketed as either single or multidose presentations. There are various recommended routes of administration for vaccines; e.g. parenteral use, oral administration following reconstitution in drinking water or in feed, respiratory/oral route by spray application. The length of time it takes for the user to administer the vaccine to the target species, and/or for the take of the vaccine by the target species (e.g. in the case of vaccine administered via drinking water) can vary considerably. The duration of this period for each vaccine is defined as the in-use shelf-life. Appropriate data are required to demonstrate that the vaccine retains an acceptable quality profile and remains efficacious throughout the in-use shelf-life.

2. Scope

This guideline outlines the data requirements which should be provided in support of claims for in-use stability of veterinary vaccines.

3. Legal basis

This guideline should be read in conjunction with the Directive 2009/9/EC.

4. Main guideline text

4.1. General concepts:

The general principles for demonstrating an appropriate in-use shelf-life will be similar regardless of the different pharmaceutical forms of the vaccine, consisting of data to demonstrate acceptable potency and microbial safety under defined conditions of use for the duration of the proposed in-use period.

For some vaccines, a recommendation to use immediately will be stated on the Summary of Product Characteristics (SPC) instead of a defined in-use shelf-life. For such products, and if it is practical to use immediately (e.g. single dose presentations), since an in-use shelf-life is not defined no data are required. The warning use immediately should not be proposed by applicants as a substitute for generating in-use stability data in circumstances whereby it is not possible to administer all the doses in a short time frame, e.g. multidose presentations containing a large number of doses.

It is important that due consideration is given when proposing an in-use shelf-life, that the proposed time will be sufficient to permit vaccination of the maximum number of target animals according to the number of doses and according to the recommended conditions of use as instructed in the SPC. The proposed in-use shelf-life shall not be longer than necessary to administer all doses to the target animals. For multidose parenteral vaccines, it is normally accepted that a shelf-life of no longer than one working day (maximum 10 hours) after first broaching is expected but a longer shelf life may be acceptable if the claim is supported by relevant in-use stability data.

4.2. Design of the in-use stability study

In support of the proposed in-use shelf-life, data from two different batches of finished product should be provided. This data shall demonstrate compliance with the critical stability-indicating parameter(s) at time zero (T0) (i.e. when the primary container is first opened or when the vaccine is manipulated into final formulation for administration), and after T0 plus the proposed in-use shelf-life (T0 +X hours). The vaccine should be tested after it has been prepared for use as per the instructions in the SPC at T0 and T0+X hours.

The conditions for the in-use stability study should be designed to mimic use of the product in practice taking into account the number of doses in the container and any dilution/reconstitution before use. For example, reconstituted vaccine which should be administered in drinking water at ambient temperatures in a poultry house, or vaccine which should be diluted in a water bath at a defined temperature for administration by immersion to fish, should not be stored in a sterile refrigerated environment during the in-use stability study. However, mimicking the conditions of use in the field will not be applicable in all cases e.g. for an inactivated suspension for injection in a sealed immediate container. The study design should be documented in the dossier and justified by the applicant.

The suitability of the tests conducted, and the acceptance limits chosen for the demonstration of in-use stability should be justified.

Data from pilot scale batches are acceptable once it is confirmed that the method of manufacture is identical to Part II of the marketing authorisation dossier, and provided that the batches conform to the finished product specifications. In-use stability data from a larger combination vaccine may be used in support of the in-use stability of a vaccine for which the composition is identical with the exception that there are fewer active ingredients.

Information on the efficacy of preservatives in other similar immunological veterinary medicinal products from the same manufacturer may be sufficient. In such cases consideration must be given to the following: differences in the in-use conditions for the similar vaccine and the test vaccine; the effect of differences in the chemical and physical characteristics of each vaccine formulation on the performance of the preservative, possible interactions between the container and the preservative for the test vaccine etc.

4.3. Potency testing

For live vaccines, potency testing should be performed at T0 and T0+X hours and the results must demonstrate that the potency will not decrease below the minimum guaranteed titre at T0+X hours. Any loss in titre during the in-use period must not be of a magnitude that would permit a vaccine to fall below the minimum guaranteed titre if it was a “worst case scenario” batch (i.e. a batch that was released at the minimum release titre and that was used near the end of the finished product shelf-life).

For inactivated vaccines, if the proposed in-use shelf-life is less than one working day (maximum 10 hours) it is acceptable to omit the potency testing from the in-use shelf-life stability study.

In the case of vaccines with a proposed in-use shelf life of more than 10 hours for which a suitable *in vitro* method is not available for the batch potency test, in-use stability data from one batch, rather than two, may be submitted with the initial application. This approach would be acceptable if the results from one batch are supportive of the proposed in-use shelf-life. Justification should be provided by the applicant for the use of only one batch in the in-use stability study, and a commitment should be made that at the next time the batch potency test is conducted for routine release of the product,

that the potency will also be tested at the end of the proposed in-use shelf-life. The complete in-use stability study should be submitted when the remaining data from the second batch are available.

4.4. Microbial Safety

The microbial safety of the vaccine should be demonstrated over the proposed in-use shelf-life. If microbial safety data is not considered necessary in support of the proposed in-use shelf-life, this should be justified by the applicant.

If an antimicrobial preservative is included in the vaccine, the efficacy of the antimicrobial preservative under in-use conditions should be demonstrated in accordance with the European Pharmacopoeia monograph *Vaccines for Veterinary Use* (0062), which includes the requirement that the efficacy of the antimicrobial preservative is tested as described in Ph. Eur. 5.1.3. At a minimum, the T0+X hours vaccine sample from the in-use stability study should be tested as described in Ph. Eur. 5.1.3 to demonstrate the efficacy of the preservative at the end of the proposed in-use shelf life.

If there is no antimicrobial preservative in the vaccine, if the product cannot be used immediately and an in-use shelf-life is proposed, the applicant should demonstrate that the product remains acceptable for its recommended period of use. In this case, data to show that there is no increase in microbiological contamination relative to an appropriate control (e.g. solvent or unmedicated drinking water) between T0 and T0+X hours may be deemed supportive.

Definitions

In-use shelf-life:	the maximum period of time recommended for use of one single presentation of a veterinary vaccine as used under recommended conditions, for which the level of quality, safety and efficacy of the vaccine has been demonstrated to be acceptable.

References

European Pharmacopoeia Monograph *Vaccines for Veterinary Use* (0062).

European Pharmacopoeia Monograph *Efficacy of Antimicrobial Preservation* (50103)