10 September 2025
EMA/CVMP/QWP/59158/2025
Committee for veterinary medicinal products (CVMP)

Guideline on in-use stability testing of veterinary medicinal products

Agreed by Quality Working Party	June 2025
Adopted by CVMP	10 September 2025
Date for coming into effect	30 September 2025

This guideline replaces and merges the 'Note for guidance on in-use stability testing of veterinary medicinal products (excluding immunological veterinary medicinal products)' (EMEA/CVMP/424/01 – FINAL) and the 'Note for guidance on maximum shelf-life for sterile medicinal products after first opening or following reconstitution' (EMEA/CVMP/198/99 – FINAL). Administrative changes are made in order to align the guideline with Regulation (EU) 2019/6 and the current EMA template for Guidance. The references to the applicable legislation and other scientific guidelines have also been updated. As no changes were made to the scientific content, no concept paper or public consultation were deemed necessary.

Keywords	***Stability, in-use shelf-life, multidose container, sterile, maximum shelf-life, veterinary medicinal product***

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1. Introduction

The purpose of in-use stability testing is to establish, where applicable, a period of time during which a multidose product may be used whilst retaining quality within an acceptable specification once the container is opened or broached. Based on this testing, a shelf-life after first opening/broaching is generally established and mentioned in the product information.

The continued integrity of products in multidose containers after the first opening/broaching is an important quality issue. This document attempts to define a framework for selection of batches, test design, test storage conditions, test parameters, test procedures etc., taking into consideration the broad range of products concerned.

This guidance should be read in conjunction with the following guidance documents:

- Development pharmaceutics for veterinary medicinal products
- Stability testing of existing active substances and related finished products
- VICH Guidelines on stability

The dossier for a multidose product should include the in-use stability data on which the in-use shelf-life is based. Alternatively, a justification as to why no in-use shelf-life is established should be included. In the case of solid oral dosage forms such as tablets, usually a justification for the absence of an in-use shelf-life will suffice. In the case of other non-sterile dosage forms, a justification based on experimental results may be necessary

2. Scope

This guideline applies to veterinary medicinal products supplied in multidose containers, where by nature of their physical form and composition, the first opening of the container may pose a risk to its contents with regard to microbiological contamination or proliferation and/or physico-chemical degradation.

In addition, this guideline also provides information on the possible maximum shelf-life after first opening or following reconstitution for sterile veterinary medicinal products.

This guideline does not apply to immunological veterinary medicinal products.

3. In-use stability study

3.1. Selection of batches

A minimum of two batches, at least pilot scale batches, should be subjected to the test. At least one of the batches used in the in-use stability test should be approaching the end of its shelf-life. If results on an aged batch are not available at the time of submission, and subject to no significant change having been observed following 6 months storage under real time and accelerated conditions, the data on an aged batch can be generated post-authorisation at the final point of the ongoing stability study. The batch number, date of manufacture and size of each batch should be stated. The container and closure of the product must be identical in all respects to that proposed for marketing. If the product is supplied in more than one container size then product in the most appropriate sized container, normally the one which poses the greatest demand on the system, should be subjected to the test.

3.2. Test design

The test should be designed as far as possible to simulate the use of the product in practice, taking into account the fill volume of the container and any dilution/reconstitution before use. At intervals comparable with those which occur in practice, volumes of the product, as indicated in the product literature, should be removed by the withdrawal methods normally used and described in the product literature. For example, for a product which is administered concurrently to a large number of animals to treat a condition which is seasonal, it may be appropriate to remove a significant proportion of the contents at the start of the test only. For a product used routinely in a companion animal practice it might be more appropriate to remove aliquots of the product from the container on a daily basis. Depending on the usage pattern of a particular product, more than one test design may be necessary.

Sampling should take place under normal environmental conditions.

The appropriate physical, chemical and microbial properties of the product susceptible to change during storage should be determined over the whole period of the proposed in-use shelf-life. If possible, testing should be performed at intermediate time points and at the end of the proposed in-use shelf-life on the final amount of product in the container.

The rationale for selection of the test design should be provided.

3.3. Test storage conditions

Throughout the in-use stability test period, the product should be stored as recommended on the product literature (SPC and package leaflet). The storage temperature, humidity and light conditions should be recorded. Any other storage conditions should be justified.

3.4. Test parameters

The appropriate physical, chemical and microbial properties of the product susceptible to change during use should be monitored. The parameters tested must be appropriate to individual formulations but examples of the types of parameters which may need to be studied are given below:

Physical: colour, clarity, closure integrity, presence of particulate matter, particle size.

Chemical: active substance level(s), antimicrobial and chemical preservative level(s), degradation product level(s), pH.

Microbial: Total viable count, antimicrobial preservative efficacy (Ph. Eur.): single challenge or repeat challenge [1], depending on the nature of the product.

3.5. Analytical procedures

The analytical procedures used in the study should be described and fully validated. Stability-indicating assays should be employed.

3.6. Presentation of results

The results should be summarised and tabulated.

If relevant, the results should be presented graphically.

[1] Repeat preservative efficacy is not usually required, except where a more rigorous test for preservative efficacy is demanded, for example for sterile products where the proposed in-use shelf-life exceeds the recommended maximum in-use shelf-life as addressed in section 5 of this guideline.

3.7. Evaluation

Conclusions reached based on the data provided should be stated. In the case of anomalous results these should be explained.

Where applicable and justified an in-use shelf-life specification should be given. Examples of where an in-use shelf-life specification would normally be considered to be applicable include:

- Products which are reconstituted prior to first use
- Products in which small, but acceptable and justified, levels of degradation occur following opening.

In-use stability data should be used to determine whether or not a declaration of an in-use shelf-life and additional storage conditions are necessary.

4. Summary of product characteristics, package leaflet and labelling

The in-use shelf-life and the special precaution(s) for storage, if applicable, should be recorded on the SPC, package leaflet and outer package as required by the QRD template.

5. Maximum in-use shelf-life of sterile products after first opening or following reconstitution

Because it is difficult to predict all the possible conditions under which the product will be opened, diluted, reconstituted and stored, etc., the user is responsible for maintaining the quality of the product that is administered to the animal.

The Applicant should conduct appropriate studies and provide the relevant information in the Product Information texts.

The Applicant should also take note of the recommendations contained in the European Pharmacopoeia, with respect to storage times and conditions for specific categories of sterile products, once opened.

5.1. Unpreserved aqueous sterile products

In general, the product information texts include statements to use the product immediately after first opening, reconstitution or dilution.

Where justified, storage at 2 to 8 °C for no longer than 24 hours may be proposed for preparations for infusion after reconstitution or dilution. Chemical and physical stability for x hours should be demonstrated.

The product information texts should include details of the in-use shelf-life for which supporting chemical and physical stability data has been provided.

For specific wording to be included in the product information, cross-reference is made to the QRD template.

5.2. Aqueous preserved sterile products and non-aqueous sterile products, e.g. oily preparations, including products containing antimicrobial preservatives or which are intrinsically self-preserving.

Chemical and physical stability for x hours/days at y °C should be demonstrated after first opening, reconstitution or dilution. Moreover, x and y should be justified from a microbiological point of view. Normally, x should not be greater than 28 days.

The product information should include details of the in-use shelf-life for which supporting data has been provided.

For specific texts to be included in the product information, cross-reference is made to the QRD template.