



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

**NOTE FOR GUIDANCE ON IN-USE STABILITY TESTING OF
VETERINARY MEDICINAL PRODUCTS (EXCLUDING IMMUNOLOGICAL
VETERINARY MEDICINAL PRODUCTS)**

ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION	16 MAY 2001
START OF CONSULTATION	17 MAY 2001
END OF CONSULTATION	1 DECEMBER 2001
REVIEWED BY QUALITY WORKING PARTY	9-11 JANUARY 2002
FINAL ADOPTION BY CVMP	13 FEBRUARY 2002
DATE OF COMING INTO EFFECT	1 SEPTEMBER 2002 ¹

¹ *The guideline applies to all new and already authorised veterinary parenteral products supplied in multidose containers. In addition, for all new Marketing Authorisation applications or relevant variation applications submitted after 01 September 2002, the guideline applies to all veterinary medicinal products packed in multidose containers*

Objective

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.

Scope

This guideline applies to all parenteral preparations supplied in multidose containers². It is also applicable to other types of 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.

Introduction

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 Notes for Guidance:

Development pharmaceuticals

Stability testing of existing active substances and related finished products

Stability testing of new drug substances and products

The registration 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 This guideline does not apply to immunological veterinary medicinal products

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.

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.

Test Storage Conditions

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

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: single challenge (Ph.Eur) or repeat challenge³, depending on the nature of the product.

Analytical Procedures

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

Presentation of results

The results should be summarised and tabulated.

If relevant, the results should be presented graphically.

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.

³ 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 according to CVMP guideline EMEA/CVMP/198/99-Final.

Labelling of the Primary Container

A suitably labelled space should be provided on the label of the primary container so that the user may, on the day of first withdrawing a dose from the container, record the date on which the product remaining in the container should be discarded. In addition if there is sufficient space on this label, the in-use-shelf-life should be stated. As the ability to include this information on the label is mainly governed by the size of the primary pack, the following general rules apply:

For multidose containers of greater than or equal to 50ml, the in-use shelf-life and a suitably labelled space for the discard date, must always appear on the label of the primary pack.

For multidose containers of less than 50 ml, a suitably labelled space for the discard date should be included on the label of the primary pack, unless it can be demonstrated that by doing so more important instructions and warnings will be rendered illegible. In this case the suitably labelled space for the discard date and the in-use shelf-life should appear on the label of the secondary pack.

Summary of Product Characteristics, Package Insert and Labelling of the Secondary Container.

The in-use shelf-life and in-use storage recommendations, if applicable, should be recorded on the SPC, package insert and outer carton, together with advice to discard any product remaining in the container at this time. The statement "Avoid introduction of contamination" should also be included.

- 1.