

## IN USE STABILITY TESTING OF VETERINARY MEDICINAL PRODUCTS (EXCLUDING IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS)

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| Additional Notes         | This note describes the method to determine the period of time (in use stability) during which a multidose product may be used following the removal of the first dose of product from the container without adversely affecting the integrity of the product. |

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# IN USE STABILITY TESTING OF VETERINARY MEDICINAL PRODUCTS (EXCLUDING IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS)

## 1. INTRODUCTION

The purpose of in use stability testing is to establish a period of time during which a multidose product may be used following the removal of the first dose of product from the container without adversely affecting the integrity of the product.

Such testing is applicable to all parenteral preparations supplied in multidose containers<sup>1</sup>. However, it is particularly important that such testing is applied if the air in the headspace of the vial is replaced with an inert gas during manufacture, or if the formulation includes an antioxidant, or a volatile antimicrobial preservative.

Testing may also be applicable to multidose oral or topical dosage forms if a specific problem in terms of stability of the product has been identified, once the container has been opened. The situation would apply for example, to an oral product in which the active ingredient, which is subject to oxidative degradation, has been packed in a well filled, oxygen-impermeable container.

The testing procedure involves the removal of aliquots as defined under test design, of the product (reconstituted if appropriate) from the container at regular intervals and the determination of physical, chemical and microbial properties of the product over the period of the proposed in use shelf life.

## 2. SELECTION OF BATCHES

A minimum of two batches should be subjected to the test. Where the chemical characteristics of a product alter significantly during storage in the sealed marketing containers, for example if the antioxidant levels in the formulation are reduced, at least one of the batches used in the in use stability test should be approaching the end of its shelf life. The batch number, date of manufacture and size of each batch should be stated. It is preferable for production scale batches to be used in the test, however development scale batches may be used if the processing is representative of that which will be used in production. 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. TEST DESIGN

The test should be designed as far as possible to simulate the use of the product in practice. 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. For

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<sup>1</sup> This guideline does not apply to immunological veterinary medicinal products.

example for a product which is administered concurrently to a large numbers 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 and then to re-examine the product at intervals up to the end of the proposed in use shelf life. 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 and then to examine the product remaining in the container at intermediate time points and at the end of the proposed in use shelf life. Depending on the usage pattern of a particular product, more than one test may be necessary.

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

#### 4. STORAGE CONDITIONS

Throughout the period of the test the product should be stored as recommended on the product literature. The storage temperature, humidity and light conditions should be recorded.

#### 5. TEST PARAMETERS

The physical, chemical and microbial properties of the product should be monitored. The tests used 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 ingredient 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 challenge, depending on the nature of the product.

#### 6. TEST PROCEDURES

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

#### 7. PRESENTATION OF RESULTS

The results should be summarised and tabulated.

#### 8. EVALUATION

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

#### 9. LABELLING OF THE PRIMARY CONTAINER

A suitably labelled space should be provided 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 the label, the in use shelf life should be stated.

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## 10. SUMMARY OF PRODUCT CHARACTERISTICS, LEAFLET AND LABELLING OF SECONDARY CONTAINERS

The in use shelf life must be recorded, together with advice to discard any product remaining in the container at this time. The statement "Avoid introduction of contamination" should also be included.