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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTE FOR GUIDANCE ON IN-USE STABILITY TESTING OF HUMAN MEDICINAL PRODUCTS

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NOTE FOR GUIDANCE ON IN-USE STABILITY TESTING OF HUMAN MEDICINAL PRODUCTS

Objective

The purpose of in-use stability testing is to establish - where applicable - a period of time during which a multidose product can be used whilst retaining quality within an accepted specification once the container is opened.

Scope

This guideline refers to medicinal products in multidose containers which - by nature of their physical form and chemical composition - due to repeated opening and closing, may pose a risk to its content with regard to microbiological contamination, proliferation and/or physico-chemical degradation once the closure system has been breached.

Introduction

The continued integrity of products in multidose containers after the first opening is an important quality issue. While this principle is acknowledged in the Ph. Eur. and EU Guidelines, no specific guidance is available on defining test design and conduct of studies to be undertaken to define in-use shelf life in a uniform fashion. Therefore, 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.

Nevertheless should this Note for guidance also be read in connection with the *Notes for guidance on Development pharmaceutics* (CPMP/QWP/155/96), *Stability testing of existing active substances and related finished products* (CPMP/QWP/556/96) *and Stability testing of new drug substances and products* (CPMP/ICH/2736/99).

The registration dossier for a multi-dose product should include either the in-use stability data on which the in-use shelf life is based or a justification why no in-use shelf life is established. This justification can also be based on experimental results.

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 should be chosen towards the end of its shelf life. If such results are not available, one batch should be tested at the final point of the submitted stability studies. The batch number, date of manufacture and size of each batch should be stated. The container and closure of the product and, if present, the medicinal device should be equivalent to that proposed for marketing.

If the product is to be supplied in more than one container size or in different strengths, the in-use stability test should be applied to the product which presents the greatest susceptibility to change. The choice of the tested product should always be justified.

Test design

As far as possible the test should be designed to simulate the use of the product in practice taking into consideration the filling volume of the container and any dilution/reconstitution before use. At intervals comparable to those which occur in practice appropriate quantities should be removed by the withdrawal methods normally used and described in the product literature. Sampling should take place under normal environmental conditions of use.

The appropriate physical, chemical and microbial properties of the product susceptible to change during storage should be determined over the 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 remaining amount of the product in the container.

Test storage conditions

The product should be stored under the conditions as recommended in the product literature (SPC and PIL) throughout the in-use stability test period.

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 tests used must be appropriate to individual dosage forms, however, examples of parameter types which may need to be studied are given below:

Physical:	colour, clarity, closure integrity, particulate matter, particle size
Chemical:	active substance assay(s), antimicrobial preservative and antioxidant content(s), degradation product level(s), pH
Microbial:	Total viable count, sterility

Analytical procedures

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

Presentation of the results

The results should be summarized 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.

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.

Labelling of the primary container

The in-use shelf life should be stated on the label. In addition (if space allows) there should be a space for the user to write the date of opening or the "use-by" date.

SPC, leaflet and labelling of the secondary container

The in-use shelf life and in-use storage recommendations - if applicable - should be included in SPC, leaflet and outer carton text.