European Medicines Agency
Inspections

London, 19 May 2005
CPMP/QWP/576/96 Rev 1
EMEA/CVMP/373/04

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)
COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

GUIDELINE ON STABILITY TESTING FOR APPLICATIONS FOR VARIATIONS TO A MARKETING AUTHORISATION

DRAFT AGREED BY QUALITY WORKING PARTY	**October 2003/ April 2004 (joint)**
ADOPTION BY CPMP/CVMP FOR RELEASE FOR CONSULTATION	**December 2003/ April 2004 (joint)**
END OF CONSULTATION (DEADLINE FOR COMMENTS)	**15 October 2004**
AGREED BY QUALITY WORKING PARTY	**February 2005**
ADOPTION BY CHMP/ CVMP	**April/ May 2005**
DATE FOR COMING INTO EFFECT	**1 December 2005**

This guideline replaces the CPMP Note for Guidance on Stability Testing for a Type II Variation to a Marketing Authorisation ref. CPMP/QWP/576/96 dated 22 April 1998, and is now also applicable to veterinary medicinal products.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 95
E-mail: QWP@emea.eu.int http://www.emea.eu.int

GUIDELINE ON STABILITY TESTING FOR APPLICATIONS FOR VARIATIONS TOA MARKETING AUTHORISATION

TABLE OF CONTENTS

GUIDELINE ON STABILITY TESTING FOR APPLICATIONS FOR VARIATIONS TO A MARKETING AUTHORISATION

Preamble

The following guideline sets out the stability testing requirements for variations to a Marketing Authorisation after approval. This guideline is an extension of the CHMP and CVMP Guidelines on Stability Testing of Existing Active Substances and Related Finished Products and the respective ICH/VICH Guidelines for New Active Substances and Drug Products. It is intended to be applied in the European Union.

The guideline seeks to exemplify the stability data required for variations to active substances and/or finished products. It is not always necessary to follow this when there are scientifically justifiable reasons for using alternative approaches.

The guideline provides a general indication on the requirement for stability testing, but leaves sufficient flexibility to encompass the variety of different practical situations required for specific scientific situations and characteristics of the material being evaluated.

In cases of variations which require generation of stability data on the finished product, the stability studies required, including commitment batches, should always be continued up to the approved shelf-life and the authorities should be informed immediately if any problems with the stability appear during storage, e.g. if outside specification or potentially outside specification.

This guideline is applicable to chemical active substances and related finished products and not to radiopharmaceuticals, biologicals and products derived from biotechnology.

Objective

The purpose of this guideline is to outline the stability data which have to be generated in case of variations.

Scope

Variations for active substances and finished products encompass a wide range of situations.

The Guideline provides general guidance on stability testing in case of type I variations. Furthermore, it addresses the information required for active substances and/or finished products in the following widely encountered cases of type II variations:

1. Change in the manufacturing process of the active substance;
2. Change in composition of the finished product;
3. Change of immediate packaging of the finished product.

The scope and design of the stability studies for variations and changes are based on the knowledge and experience acquired on active substances and finished products.

The available information must be taken into account such as:

a) For active substances:

- the stability profile including the results on stress testing;
- the supportive data;
- the primary data of accelerated and long term testing.

b) For finished products:

- the supportive data;

- the primary data of accelerated and long term testing.

In all cases of variations, the applicant has to investigate whether the intended change will have an impact or not on the quality characteristics of active substances and/or finished products and consequently on their stability.

When stability data are required, the choice of test conditions defined in this guideline refers to the CHMP/ICH Guideline on Stability Testing of New Drug Substances and Products, the CHMP/QWP Guideline on Stability Testing of Existing Active Substances and Related Finished Products, the CVMP/VICH Guideline on Stability Testing of New Veterinary Drug Substances and Medicinal Products, and the CVMP/QWP Note for Guidance on Stabilty Testing of Existing Active Substances and Related Finished Products, respectively. Where appropriate, the concept of bracketing and matrixing as described in the CHMP/ICH Note for Guidance on Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products may be applied across related products.

1. TYPE I VARIATIONS

If a variation to a marketing authorisation fulfils the conditions defined in Commission Regulations EC 1084/2003 or 1085/2003 for Type I variations, and if stability data are required, the minimum set of data to be submitted with the variation is defined in the Guideline on Dossier Requirements for Type IA and Type IB Notifications. The results of these studies, covering the requested time period as defined in above guideline, using accelerated and long-term testing conditions, should be compared to the results of studies performed on the unchanged active substance/finished product in order to ensure that the change does not negatively impact the stability profile, i.e. that the specification limits of the active substance/finished product will still be met at the end of the proposed retest period/shelf-life. The comparison data for the unchanged product may come from earlier studies, and need not necessarily be collected in combination with the study on the changed product.

2. TYPE II VARIATIONS

European Commission Regulations EC 1084/2003 and 1085/2003 define a Type II variation as being a variation which cannot be deemed to be a minor variation or an extension of the marketing authorisation. Consequently, any variation not listed in Annex I or Annex II to above regulations is classified as a Type II variation. Furthermore, any variation listed in Annex I which does not meet the conditions laid down in the Annex does not become a Type IB variation, unless this option is provided for and the defined conditions are met, but a Type II variation.

2.1. Change in the Manufacturing Process of the Active Substance

In case of variations to the manufacturing process of the active substance, the following approaches may be considered as acceptable:

If the quality characteristics (e.g. physical characteristics, impurity profile) of the active substance are changed in such a way that stability may be compromised, comparative stability data are required in accelerated and long term testing conditions, on the active substance before and after the change:

- for active substances known to be stable: three months on one batch of at least pilot scale (see Annex I for the definition of stable active substance).
- for active substances known to be unstable: six months on three batches of at least pilot scale.

If the quality characteristics of the active substance are changed in such a way that it may impact the stability of the finished product, additional stability data on the finished product, in accelerated and long term testing conditions, three months on two batches on at least pilot scale, may be required.

2.2. Change in composition of the finished product

In case of a change in the composition of the finished product, the following approaches may be considered as acceptable:

For conventional dosage forms (e.g. conventional release solid dosage form, solutions) and when the active substance is known to be stable, comparative stability data, 6 months duration, long term and accelerated testing conditions on two pilot scale batches are required.

For critical dosage forms (e.g. prolonged release form) or when the active substance is known to be unstable, comparative stability data, 6 months duration long term and accelerated stability testing conditions on three pilot scale batches are required.

2.3. Change in immediate packaging of the finished product

In case of a change to the immediate packaging of the finished product the following approach may be considered as acceptable:

In the case of less protective packaging or when a risk of interaction occurs, mainly for semi-solid or liquid dosage forms, comparative stability data are required using accelerated and long term testing conditions of six months duration on three pilot scale batches of the finished product.

3. COMMITMENT BATCHES

For all Type IB variations that require the generation of stability data on the finished product, adequate follow up studies on commitment batches need to be performed.

For all Type II variations that require the generation of stability data on the finished product, at least the first production scale batch manufactured according to the approved variation should be placed on long term stability testing using the same stability testing protocol as described above unless it has already been submitted as part of the variation application. Stability studies need to be continued to cover the entire shelf-life. The results of these stability studies should be made available on request and the authorities should be informed if any problems appear with the stability studies.

ANNEX I

An active substance is considered as stable if it is within the initial specifications when stored at 25°C/ 60 % RH or 30°C/60% RH or 65% RH, respectively, (2 years) and 40°C/75 %RH (6 months).

ANNEX II

Where the data submitted, long term 25ºC/60% RH or 30°C/60% RH or 65% RH, respectively, and accelerated 40ºC/75% RH or, in case of aqueous products in semi-permeable containers, the respective storage conditions defined in the CHMP and CVMP Guidelines on Stability Testing of Active Substances and Related Finished Products, show that there is no adverse effect on the stability of the active substance/finished product, the retest period/shelf life originally granted can normally be retained, based on comparison with the original data submitted. However, where the data demonstrate an adverse change in product stability, a new shelf life must be assigned. Based on a case-by-case decision, extrapolation of data may be applied.

If real time data are supported by results from studies conducted under accelerated or intermediate storage conditions, the retest period/shelf-life may be extended beyond the end of real time studies. Normally, extrapolation to twice the length of the real time studies can be accepted. However, the maximum shelf-life justified by extrapolation should not exceed 3 years. The degree up to which extrapolation will be acceptable following to a change to the active substance or finished product that shows an adverse effect to the stability will largely depend on the change over time, variability of data observed, proposed storage conditions and extent of statistical analyses performed. It will always have to be a case-by-case decision. For more detailed information on statistical evaluation of stability data please refer to the CHMP/ICH Note for Guidance on Evaluation of Stability Data; similar principles are also applicable to veterinary medicinal products.