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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTE FOR GUIDANCE ON STABILITY TESTING FOR A TYPE II VARIATION TO A MARKETING AUTHORISATION

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STABILITY TESTING FOR A TYPE II VARIATION TO A MARKETING AUTHORISATION

Preamble

The following guideline sets out the stability testing requirements for Variations to a marketing Authorisation, type II, after approval. This guideline is an extension of the CPMP guideline on Stability testing of existing active substances and related finished products. It is intended to be applied in the European Union.

The guideline seeks to exemplify the stability data required for Variations to marketing Authorisation, type II, for 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.

The Stability studies required should always be continued up to the approved re-test period (active substance) or shelf-life (finished product) and the authorities should be informed if any problems with the stability appear during storage.

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 in well defined cases of type II Variations the stability data which has to be submitted to the Competent authorities.

Scope

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

The guideline addresses the information required for active substances and/or finished products in the following widely encountered cases of 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.

The applicant has to investigate whether Variations have an impact or not on the quality characteristics of active substances and/or finished products and consequently on their stability.

When stability data is required, the choice of test conditions defined in this guideline refers to the CPMP/ICH guideline on Stability Testing of New Active Substances and Medicinal Products.

1. CHANGE IN THE MANUFACTURING PROCESS OF THE ACTIVE SUBSTANCE

In case of variations the following approaches may be considered as acceptable:

a) Variations concerning modifications affecting one or more steps of the same route of synthesis.

If the quality characteristics (e.g. physical characteristics, impurity profile) of the active substance are adversely changed, comparative stability data, in accelerated and long term testing conditions, on the active substance coming from the same process before and after Variation are required:

- for active substance known to be stable: three months on one batch of at least pilot scale.
- for active substance known to be unstable: six months on three batches of at least pilot scale.

In the case of variations to the final step of the manufacturing process of the active substance (e.g. new solvent, conditions of crystallisation), additional stability data on the finished product, in accelerated and long term testing conditions, three months on two pilot scale batches, may be required for solid dosage forms for which a physical characteristic of the active substance may have an impact on stability.

b) Variation concerning a change in route of synthesis of an active substance.

Comparative stability data are required between active substance coming from previous and new synthesis, in accelerated and long term testing conditions, six months on three batches, at least pilot scale.

In case of a change in specification of the active substance coming from the new synthesis and if the change can affect the stability of the finished product (e.g. physical characteristics, increase of the level of degradation products), additional stability data on the related finished products(s), in accelerated and long term testing conditions, three months on at least two pilot scale batches, may be required.

2. CHANGE IN COMPOSITION OF THE FINISHED PRODUCT

In case of a change in the composition of the finished product, not covered by the European Commission Guideline III/5783/93 (Type I variations), 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 is 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 is required.

3. CHANGE ON IMMEDIATE PACKAGING OF THE FINISHED PRODUCT

In all cases of change on immediate packaging of the finished product, not covered by the European Commission Guideline III/5783/93 (type I variations) the following approaches 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.

4. FOLLOW UP STUDIES

For all of the above variations (1 - 3), the first three production scale batches manufactured following approval of the variation should be placed on long term stability testing using the same stability testing protocols as described above. The results of the stability studies when available should be submitted to the Competent Authorities.

ANNEX I

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

ANNEX II

Where the data submitted, long term 25ºC /60% RH and accelerated 40ºC/75% RH, show that there is no adverse effect on the stability of the product, the 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. In such circumstances extrapolation of data may be applied

Extrapolation of data

If real time data is supported by results from accelerated studies the 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.