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CPMP/QMP/576/96 Guideline

Stability Testing for a Type II Variation to a Marketing Authorisation CPMP/QMP/576/96

Comments for its application

Preamble

The guideline seeks to exemplify the stability data required for variations to Marketing Authorisation, type II, for active substances and/or finished products

Stability studies required should always be continued up to approved re-test period (active substance) or shelf life (finished product)

Scope of the guideline

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

1. **Change in the manufacturing process or 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

❒ **For active substance:**

- The stability profile including results of stress testing,
- The supportive data,
- The primary data of accelerated and long term testing

❒ **For finished products:**

- The supportive data
- The primary data of accelerated and long term testing.

1. Changes in the manufacturing process of the drug substance

Change	Type	Requirements
Manufacturer of active substance	I	• Specifications, synthetic route and quality control procedures are the same. - Batch analysis data of at least two batches minimum pilot scale.
Minor change of manufacturing process	I	• Specifications not adversely affected. No change in physical properties. • No new impurities or change in level of impurities. - Batch analysis data of at least two batches minimum pilot scale.
Batch size of active substance	I	• No influence on consistency of production or physical properties. - Batch analysis data minimum one production batch manufactured to both the currently approved and the proposed size.

1. Changes in the manufacturing process of the drug substance

Change	Type	Requirements
Change is Specifications of drug substance	I	• Specifications must be tightened or addition of new test and limits
		• Comparative dissolution profile data for the finished product on at least one pilot production batch complying with current and proposed specifications. • Batch analysis data for at least 2 pilot/ production batches
Modifications affecting one or more steps of the same route of synthesis. Quality characteristics (physical characteristics, impurity profile) are adversely changed.	II	• Comparative stability data, accelerated and long term conditions, on active substance before and after variation: - stable active substance: three months one batch pilot scale - unstable active substance: six months three batches pilot scale

1.Changes in the manufacturing process of the drug substance

Change	Type	Requirements
Modifications to final step of manufacturing process, e.g. new solvent, conditions of crystallisation	II	• Accelerated and long-term stability testing with finished product three months on two pilot scale batches, if physical characteristic of active substance may have impact on stability.
Change in route of synthesis	II	• Comparative stability testing accelerated and long term, six months three batches pilot scale (new synthesis). • If change in specifications which can effect stability of finished product, accelerated and long-term testing on at least three pilot scale batch of finished product 3 months.

2. Change in composition of the finished product

The available information must be taken into account

- the supportive data
- the primary data of accelerated and long term testing

The applicant has to investigate whether the variations have an impact on the characteristics of the finished product and consequently on the stability.

Change	Type	Requirements
Replacement of an excipient with a comparable excipient	I	• No change in dissolution profile for solid dosage forms. • Comparative dissolution profile data on at least one representative pilots scale batch in new and old composition. • Release- and shelf life specifications have not been changed. • Commitment that appropriate stability studies will be performed (follow up)
Deletion or replace-ment of colorant	I	• Release- and shelf life specifications have not been changed. • Commitment that appropriate stability studies will be performed (follow up)

2. Change in composition of the finished product

Change	Type	Requirements
Change in coating weight of tablets or change in weight of capsule shell	I	• Comparative dissolution profile data of one pilot scale batch new and old composition. • Release- and self life specifications have not been changed
Minor changes in manufacture or the medicinal product	I	• Specifications are not adversely affected. • Comparative dissolution data of 1 representative production batch and the last 3 batches from the previous process. • Release- and shelf life specifications have not been changed
Batch size of finished product	I	• Change does not affect consistency of production. • Batch analysis data of one production batch manufactured to previous and proposed batch size. • Release- and shelf life specifications have not been changed
Change in specification	I	• Specifications must be tightened or addition of new tests and limits • Comparative dissolution profile when appropriate • Comparative batch analysis data for at least 2 production scale batches

2. Change in composition of the finished product

Change	Type	Requirement
Extension of shelf life as foreseen at time of authorisation	I	• Stability studies have been done to the protocol which was approved at the time of the issue of the marketing authorisation
Change in test procedures	I	• Specifications are not adversely affected. • Results or validation show new test procedure to be at least equivalent to the former procedure.
Change of dimensions of tablets, capsules. .without change of quantitation composition and mean mass.	I	• No change in dissolution profile • Comparative dissolution data on one batch of previous an proposed dimensions. • Release- and shelf life specifications have not been changed.
Change in composition exceeding type I variations	II	• Conventional dosage forms with stable active substance (within specifications 2 years 25°C/60%, 6 months 40°C/75%): - Comparative stability testing, accelerated and long-term, 6 months, 2 pilot scale batches. • Critical dosage forms with unstable active substance: - Comparative stability testing accelerated and long – term testing,3 months, 3 pilot scale batches • Follow-up studies, three production scale batches 6 months accelerated and long term.

3. Changes on immediate packaging of finished product

In the following table the requirements are listed:

Change	Type	Requirements
Test procedure of immediate packaging	I	• According to validation data new test procedure at least equivalent
Changes exceeding type I. Less protective packaging or when risk of interaction mainly for semi-solid and liquid dosage forms	II	• Comparative accelerated and Iong-term testing for 6 months with 3 pilot scale batches. • Follow-up studies with three post-approval production batches accelerated and Iong term testing 6 months.

If submitted data 2560, 40°C/75% show no adverse effect on the stability, the shelf life originally granted ca be retained.