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Guideline on stability testing for applications for variations to a marketing authorisation

Draft

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Guideline on stability testing for applications for variations to a marketing authorisation

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Executive summary

The following guideline provides guidance on the stability data which have to be generated in order to support a variation to a Marketing Authorisation. The guideline provides general guidance on stability testing in case of type I (A and B) variations and addresses the data requirements for widely encountered cases of type II variations.

1. Introduction (background)

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.

2. Scope

The purpose of this guideline is to outline the stability data which have to be generated in case of variations. It is applicable to chemical active substances and related finished products, herbal drugs, herbal drug preparations and related herbal medicinal products, however not to radiopharmaceuticals, biologicals and products derived from biotechnology.

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 (A and B) variations, furthermore, it addresses the information required for active substances and/or finished products in widely encountered cases of type II variations as listed in section 6.

3. Legal basis

This guideline has to be read in conjunction with Regulation No 1234/2008 and the introduction and general principles (4) and annex I to Directives 2001/82 and 2001/83 as amended.

4. General requirements

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.

The scope and design of the stability studies for variations and changes are based on the knowledge and experience acquired on the 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 Stability Testing of Existing Active Substances and Related Finished Products, respectively. Where appropriate, the concept of bracketing and matrixing as described in the CHMP/ICH and the CVMP/VICH Note for Guidance on Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products may be applied across related products.

Where extrapolation of data are applicable, see Annex II for further information.

5. Type I variations

If a variation to a marketing authorisation fulfils the conditions defined in Commission Regulation EC 1234/2008 for Type IA variations, and if stability data are required, the minimum set of data to be submitted with the variation is defined in the Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products. 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.

Type IB is the new default category under the new variations Regulation. As far as the associated classification guideline is concerned, some examples of different types of Type IB changes have been included in the guideline, along with recommended documentation. Where a change may impact on stability, the required satisfactory stability data requirements at the time of submission are specified in the guideline. In case of other Type IB by default changes, which are not specifically described in the classification guideline, the required stability data has to be decided on a case by case basis. However, consideration should be given to specified requirements for any other similar changes which have actually been included as examples in the guideline.

6. Type II variations

European Commission Regulations EC 1234/2008 define Type II variation as major variations which have the highest potential impact on the quality, safety or efficacy of medicinal products. Type II

variations are defined in the Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products. However data to be submitted with these variations are not defined in the majority of cases.

6.1. Introduction of a new manufacturer of the active substance that is supported by an ASMF (B.I.a.1.b)

In case of an introduction of a new manufacturer of the active substance that is supported by an ASMF stability data should be part of the applicants part of the ASMF. In cases where no retest period is fixed (according to the relevant guidelines) the active substance has to be tested immediately prior use.

If the quality characteristics/impurity profile 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 conditions, six months on two batches on at least pilot scale, may be required.

6.2. Change in the manufacturer of a starting material / reagent / intermediate or the active substance that uses a substantially different route of synthesis or manufacturing conditions, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability (B.I.a.1.c)>

In case of such a variation 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, six months on two batches on at least pilot scale, may be required.

6.3. Change in the manufacturing process of the active substance (B.I.a.2.b; B.I.a.2.d)

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, six months on two batches on at least pilot scale, may be required

6.4. Change in immediate packaging of the active substance (B.I.c.1.b)

In case of a change to the immediate packaging of a sterile active substance the following approach may be considered as acceptable:

Comparative stability data are required using accelerated and long term testing conditions of six months duration on at least 2 pilot scale batches of the active substance.

6.5. Change in composition of the finished product (B.II.a.3.b.2)

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.

6.6. Change in coating weight of oral dosage forms (B.II.a.4.b)

In case of a change in the coating weight of oral dosage forms, the following approaches may be considered as acceptable:

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.

6.7. Change in the manufacturing process of the finished product (B.II.b.3.b, 3.d-e)

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

If the quality characteristics (e.g. physical characteristics, impurity profile) of the active substance or an excipient 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 drug product before and after the change:

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.

6.8. Change in the batch size of the finished product (B.II.b.4.d)

In case of variations to the batch size of the drug product, the following approaches may be considered as acceptable:

If the quality characteristics (e.g. physical characteristics, impurity profile) of the active substance or an excipient 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 drug product before and after the change:

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.

6.9. Change in immediate packaging of the finished product (B.II.e.1a.3., B.II.e.1a.4. B.II.e.1.b. 2.)

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 batches of the finished product.

7. Commitment batches

For all Type IA and 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 in the original application 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.

References

Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7)

Guideline on Stability Testing of New Drug Substances and Products (CPMP/ICH/2736/99-ICH Q1A)

Guideline on Stability Testing of New Veterinary Drug Substances and Medicinal Products (CVMP/VICH/899/99 Rev.1-VICH GL43)

Guideline on Stability Testing of Existing Active Substances and Related Finished Products (CPMP/QWP/122/02 Rev. 1 corr)

Note for Guidance on Stability Testing of Existing Active Substances and Related Finished Products (EMEA/CVMP/QWP/846/99-Rev.1)

Note for Guidance on Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products (CPMP/ICH/4104/00-ICH Q1D)

Bracketing and matrixing designs for stability testing of new veterinary drug substances and medicinal products (EMEA/CVMP/VICH/581467/2007-VICH GL45)

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/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/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.