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Committee for Medicinal Products for Human Use (CHMP)

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

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This guideline replaces Guideline on stability testing for applications for variations to a marketing authorisation previous version (EMA/CHMP/CVMP/QWP/441071/2011- Rev.2).

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Executive summary

This 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 for type IA and type IB variations and addresses the data requirements for common type II variations.

1. Introduction (background)

This guideline describes the stability testing requirements for variations to a marketing authorisation after approval. This guideline is an extension of the CHMP Guidelines on stability testing of existing active substances and related finished products and the respective ICH Guidelines for new active substances and finished products. It is intended to be applied in the European Union.

The guideline seeks to illustrate the stability data required for variations to active substances and/or finished products. It is not always necessary to comply with this guideline when there are scientifically justifiable reasons for using alternative approaches (e.g., quality by design concept). However, the stability data outlined in this guideline reflects the usual expectation of the regulators.

While the guideline provides a general indication on the requirement for stability testing, it allows 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 substances, herbal preparations and related herbal medicinal products. Radiopharmaceuticals, biologicals/immunologicals and products derived from biotechnology are not within the scope of this guideline.

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 common type II variations as listed in section 6.

3. Legal basis

This guideline should be utilised in conjunction with Commission Regulation (EC) No 1234/2008 as amended and the introduction and general principles section (4) of Annex I to Directives 2001/83 as amended.

4. General requirements

In cases of variations which require generation of stability data on the finished product or the active substance, the stability studies required, including commitment batches, should always be continued up to the approved shelf-life / retest period 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 of 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 of stress testing, if applicable (except herbals);
- the supportive data;
- the primary data of long term and accelerated* testing.

b) For finished products:

- the supportive data;
- the primary data of long term and accelerated* testing.

In all variations, the applicant assesses whether the intended change has the potential to impact the quality characteristics and stability of the active substances and/or the finished products and consequently on their stability.

When stability data are required, the choice of test conditions, defined in this guideline refers to

- CHMP/ICH Guideline on Stability Testing of New Drug Substances and Products,
- CHMP/QWP Guideline on Stability Testing of Existing Active Substances and Related Finished Products,

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.

The results of stability studies of the varied active substance/finished product, including the requested time period as defined below, using long term and accelerated* testing conditions, should be compared to studies performed on the unchanged active substance/finished product. This ensures 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 of the unchanged product submitted with the variation may come from previous studies.

In relation to herbal substances, herbal preparations and related herbal medicinal products the guideline on quality of herbal medicinal products / traditional herbal medicinal products (EMA/HMPC/CHMP/CVMP/ 201116/2005 Rev. 3), the guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products / traditional herbal medicinal products (EMA/HMPC/CHMP/CVMP/162241/2005 Rev. 3) should also apply. The testing of herbal substances and herbal preparations, testing at accelerated storage conditions or at the intermediate storage conditions may be omitted if justified by the applicant and if the storage conditions below 25° C are clearly labelled on the product.

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

5. Type I variations

If a variation to a marketing authorisation fulfils the definition in the Commission Regulation (EC) No 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 Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and on the documentation to be submitted pursuant to those procedures.

A Type IB variation is the default category in the Commission Regulation (EC) No 1234/2008 for a variation which is not an extension and whose classification is undetermined after application of the rules provided in Commission Regulation (EC) No 1234/2008. The associated classification guideline provides examples of different types of Type IB changes that have been included in the guideline with recommended documentation. Where a change may impact stability, the required stability data at the time of submission are specified in the guideline. In 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

The Commission Regulation (EC) No 1234/2008 defines Type II variations as major variations which is not an extension and which may have a significant impact on the quality, safety or efficacy of medicinal product concerned. Type II variations are defined in the Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of the Commission Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and on the documentation to be submitted pursuant to those procedures. However, data to be submitted with these variations are not defined in the majority of cases.

The following Type II variations refer to specific Type II variations as outlined in the Guidelines mentioned above.

The stability data outlined below should be part of the documentation at submission of the variation.

6.1. (Q.I.a.1.b) Change in the manufacturing site of a starting material / intermediate used in the manufacturing process of the active substance or change in the manufacturing site (including where relevant quality control testing sites) of the active substance: Addition or replacement of a manufacturing site of an active substance that requires significant update to the relevant active substance section of the dossier, where a substantially different route of synthesis or manufacturing conditions is used, 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

In relation to stability data of the active substance, the recommendations given in the guideline on stability testing of existing active substances and finished products should be utilised.

If the quality characteristics of the active substance are changed in a way that may impact the stability of the finished product, additional stability data on the finished product, in long term and accelerated*

testing conditions, six months data on at least two batches of at least pilot scale batch size are recommended.

6.2. (Q.I.a.1.f) Change in the manufacturing site of a starting material / intermediate used in the manufacturing process of the active substance or change in the manufacturing site (including where relevant quality control testing sites) of the active substance: Addition of a manufacturing site of the active substance supported by an Active Substance Master file (ASMF)

In case of an introduction of a manufacturer of the active substance that is supported by an ASMF stability data should be included in the applicant's part of the ASMF.

In relation to stability data, of the active substance, the recommendations given in the guideline on stability testing of existing active substances and finished products should be utilised.

If the quality characteristics/impurity profile of the active substance are changed in a way that may impact the stability of the finished product, additional stability data on the finished product, in long term and accelerated* conditions, six months data on at least two batches of at least pilot scale batch size are recommended.

6.3. (Q.I.a.2.b) Changes in the manufacturing process of the active substance, intermediate of an active substance or starting material for biological active substance: Major change to the manufacturing process which may have a significant impact on the quality, safety or efficacy of the finished product

In 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 a way that stability may be compromised, comparative stability data are recommended in long term and accelerated* testing conditions, on the active substance before and after the change:

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

If the quality characteristics of the active substance are changed in a way that may impact the stability of the finished product, additional stability data on the finished product, in long term and accelerated* testing conditions, six months data on at least two batches of at least pilot scale batch size are recommended.

6.4. (Q.I.c.1.b) - Change in immediate packaging of the active substance: Change in immediate packaging of sterile liquid active substances

(Note: According to the scope this guideline is not applicable to biological/immunological active substances).

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

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

6.5. (Q.II.a.3.b.2) Change in composition (excipients) of the finished product: Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product (for example, biological excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE).

(Note: According to the scope this guideline is not applicable to biological/immunological active substances).

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 in duration, long term and accelerated* testing conditions on at least two batches of at least pilot scale are recommended.

For critical dosage forms (e.g. modified release form) or when the active substance is known to be unstable, comparative stability data 6 months in duration, long term and accelerated* stability testing conditions on at least three primary batches are recommended. Two of three batches should be at least pilot scale; the third batch may be smaller.

6.6. (Q.II.a.4.c) Change in coating weight of oral dosage forms or change in weight of capsule shells: modified or prolonged release pharmaceutical forms where the coating or capsule shell is a critical factor for the release mechanism

In variations to the coating weight of oral dosage forms, the following approach may be considered as acceptable:

Comparative stability data, 6 months in duration, long term and accelerated* stability testing conditions on at least three primary batches are recommended. Two of three batches should be at least pilot scale; the third batch may be smaller.

6.7. (Q.II.a.5) Change in concentration of a single-dose, total use parenteral product, where the amount of the active substance per unit dose (i.e. the strength) remains the same

In variations in concentration of single-dose, total use parenteral product, the following approaches may be considered as acceptable:

Comparative stability data, 6 months in duration, long term and accelerated* stability testing conditions on at least three primary batches are recommended. Two of three batches should be at least pilot scale; the third batch may be smaller.

6.8. (Q.II.b.1.c) Change in the manufacturing site for part or all of the manufacturing process of the finished product (except for batch release and batch control testing sites): Addition or replacement of a site for any manufacturing operation(s) of finished products manufactured by complex or novel manufacturing processes

(Note: According to the scope this guideline is not applicable to biological/immunological active substances and related finished products).

In variations (replacement or addition) to a manufacturing site for part or all of the manufacturing process of the finished product, the following approaches may be considered as acceptable:

If the quality characteristics (e.g. physical characteristics, impurity profile) of the finished product are changed in a way that stability may be compromised, comparative stability data are recommended in long term and accelerated* testing conditions, on the finished 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 in duration, long term and accelerated* testing conditions on at least two batches of at least pilot scale are recommended.

For critical dosage forms (e.g. modified release form) or when the active substance is known to be unstable, comparative stability data, 6 months in duration, long term and accelerated* stability testing conditions on at least three primary batches are recommended. Two of three batches should be at least pilot scale; the third batch may be smaller.

6.9. (Q.II.b.3.b) Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product: Major changes to a manufacturing process of the finished product that may have a significant impact on the quality, safety and efficacy of the finished product

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

If the quality characteristics (e.g. physical characteristics, impurity profile) of the finished product are changed in a way that stability may be compromised, comparative stability data are recommended in long term and accelerated* testing conditions, on the finished 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 in duration, long term and accelerated* testing conditions on at least two batches of at least pilot scale are recommended.

For critical dosage forms (e.g. modified release form) or when the active substance is known to be unstable, comparative stability data, 6 months in duration, long term and accelerated* stability testing conditions on at least three primary batches are recommended. Two of three batches should be at least pilot scale; the third batch may be smaller.

6.10. (Q.II.b.3.c) - Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product: Introduction of a non-standard terminal sterilisation method

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

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

For conventional dosage forms (e.g. solutions) and when the active substance is known to be stable, comparative stability data, 6 months in duration, long term and accelerated* testing conditions on at least two batches of at least pilot scale are recommended.

For critical dosage forms (e.g. suspensions or emulsions for injection) or when the active substance is known to be unstable, comparative stability data, 6 months in duration, long term and accelerated* stability testing conditions on at least three primary batches are recommended. Two of three batches should be at least pilot scale; the third batch may be smaller.

6.11. (Q.II.b.3.d) Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product: introduction of, or change in, an overage that is used for the active substance

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

If the quality characteristics (e.g. content of active substance) of the finished product are changed in a way that stability may be compromised, comparative stability data are recommended in long term and accelerated* testing conditions, on the finished 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 in duration, long term and accelerated* testing conditions on at least two batches of at least pilot scale are recommended.

For critical dosage forms (e.g. modified release form) or when the active substance is known to be unstable, comparative stability data, 6 months in duration, long term and accelerated* stability testing conditions on at least three primary batches are recommended. Two of three batches should be at least pilot scale; the third batch may be smaller.

6.12. (Q.II.b.4.d) Change in the batch size (including batch size ranges) of the finished product: The change relates to all other pharmaceutical forms manufactured by novel or complex manufacturing processes

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

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

For conventional dosage forms manufactured by a complex manufacturing process and when the active substance is known to be stable, comparative stability data, 6 months in duration, long term and accelerated* testing conditions on at least two batches of at least pilot scale are recommended.

For critical dosage forms (e.g. modified release form) or when the active substance is known to be unstable, comparative stability data, 6 months in duration, long term and accelerated* stability testing conditions on at least three primary batches are recommended. Two of three batches should be at least pilot scale; the third batch may be smaller.

6.13. (Q.II.e.1.a.3) Change in immediate packaging of the finished product: Change in qualitative and quantitative composition of an approved container: Sterile liquid finished products

(Note: According to the scope this guideline is not applicable to biological/immunological active substances and related finished products).

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 for a sterile medicinal product, comparative stability data are recommended using long term and accelerated* testing conditions of six months in duration on at least three primary batches of the finished product. Two of three batches should be at least pilot scale; the third batch may be smaller.

6.14. (Q.II.e.1.a.4) Change in immediate packaging of the finished product: Change in qualitative and quantitative composition of an approved container: The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.

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 recommended using long term and accelerated* testing conditions of six months in duration on at least three primary batches of the finished product. Two of three batches should be at least pilot scale; the third batch may be smaller.

6.15. (Q.II.e.1.b.2) Change in immediate packaging of the finished product: Change in type of container or addition of a new container: Sterile finished products

(Note: According to the scope this guideline is not applicable to biological/immunological active substances and related finished products).

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 recommended using long term and accelerated* testing conditions of six months in duration on at least three primary batches of the finished product. Two of three batches should be at least pilot scale; the third batch may be smaller.

6.16. (Q.II.e.2) Change in shape or dimensions of the container or closure (immediate packaging)

If a change to the immediate packaging of the finished product may have a significant impact of the stability of the finished product, a type II variation under Q.II.e.1, Q.II.e.2 or Q.IV.2 should be considered.

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

For conventional dosage forms manufactured by a complex manufacturing process and when the active substance is known to be stable, comparative stability data, 6 months in duration, long term and accelerated* testing conditions on at least two batches of at least pilot scale are recommended.

For critical dosage forms (e.g. modified release form) or when the active substance is known to be unstable, comparative stability data, 6 months in duration, long term and accelerated* stability testing conditions on at least three primary batches are recommended. Two of three batches should be at least pilot scale; the third batch may be smaller.

6.17. (Q.II.e.6.c) Change in pack size of the finished product: Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal product

(Note: According to the scope this guideline is not applicable to biological/immunological active substances and related finished products).

In case of such a change to the pack size of the finished product the following approach may be considered as acceptable:

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

Comparative stability data are recommended using long term and accelerated* testing conditions of six months in duration on at least three primary batches of the finished product. Two of three batches should be at least pilot scale; the third batch may be smaller.

7. Commitment batches

For Type IA and IB variations that require the generation of stability data on the finished product, adequate follow up studies on commitment batches are necessary.

For 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 protocol. The stability testing protocol is as described in the original application unless it has previously been varied. 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

Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of the Commission Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and on the documentation to be submitted pursuant to those procedures (OJ C, C/2025/5045, 22.9.2025)

Guideline on Stability Testing of New Drug Substances and Products (CPMP/ICH/2736/99-ICH Q1A (R2))

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

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

Note for Guidance on Evaluation of Stability Data (CPMP/ICH/420/02)

Guideline on quality of herbal medicinal products / traditional herbal medicinal products (EMA/HMPC/CHMP/CVMP/ 201116/2005 Rev. 3)

Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products / traditional herbal medicinal products (EMA/HMPC/CHMP/CVMP/162241/2005 Rev. 3)

*according to ICH conditions; where appropriate; intermediate storage conditions, if applicable

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 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, in those cases in which long-term and accelerated data show little or no change over time and little or no variability the proposed retest period can be extrapolated up to twice but should not be more than 12 months beyond the period covered by long–term data. 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.