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Guideline on stability testing for applications for variations to a marketing authorisation for veterinary medicinal products

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This guideline replaces the Guideline on stability testing for applications for variations to a marketing authorisation (EMA/CHMP/CVMP/QWP/441071/2011- Rev.2) for veterinary medicinal products. For human medicinal products EMA/CHMP/CVMP/QWP/441071/2011- Rev.2 still applies.

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Guideline on stability testing for applications for variations to a marketing authorisation for veterinary medicinal products

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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 for veterinary medicinal products. The guideline provides general guidance on stability testing for variations not requiring assessment (VNRA) and variations requiring assessment (VRA).

1. Introduction (background)

This guideline describes the stability testing requirements for variations to a marketing authorisation for veterinary medicinal products after approval. This guideline is an extension of the CVMP Guidelines on stability testing of existing active substances and related finished products and the respective VICH Guidelines for new active substances and drug products.

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 requirements 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 for veterinary use. 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 variations requiring and not requiring assessment.

3. Legal basis

This guideline should be utilised in conjunction with the Veterinary Medicinal Products Regulation (Regulation (EU) 2019/6), the Commission Implementing Regulation (EU) 2021/17 establishing a list of variations not requiring assessment and the Guidance on the details of the classification of variations requiring assessment (EMA/CMDv/7381/2021).

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

- the CVMP/VICH Guideline on Stability Testing of New Veterinary Drug Substances and Medicinal Products (VICH GL3)
- and the CVMP/QWP Guideline on Stability Testing of Existing Active Substances and Related Finished Products (EMA/CVMP/QWP/709423/2022), respectively.

Where appropriate, the concept of bracketing and matrixing as described in the CVMP/VICH Guideline on Bracketing and Matrixing Designs for Stability Testing of Veterinary Drug Substances and Medicinal Products (VICH GL45) 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), 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) 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. Variations not requiring assessment

If a variation to a marketing authorisation fulfils the conditions defined in the Commission Implementing Regulation (EU) 2021/17 establishing a list of variations not requiring assessment and if

stability data are required, the minimum set of data to be submitted with the variation is defined within this Commission Implementing Regulation.

6. Variations requiring assessment

Variations requiring assessment are listed in the Guidance on the details of the classification of variations requiring assessment (EMA/CMDv/7381/2021). These variations have different levels of complexity and thus supporting data for particular variations will depend on the exact nature of the change.

For certain variations requiring assessment, typically with reduced timetable (VRA-R), recommended documentation is listed in the guidance. Where a change may impact stability, the required stability data at the time of submission are specified. For the VRA-R "z"-variations, which scopes are not specifically described in the classification guidance, 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 in the guidance.

For the other variations requiring assessment, typically with standard or extended timetable (VRA-S and VRA-E), data to be submitted with these variations are not defined in the guidance in the majority of cases. The stability data outlined below should be part of the documentation at submission of these variations.

6.1. (F.I.a.1.a) Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. certificate of suitability is part of the approved dossier: Introduction of a manufacturer of active substance supported by an 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 related finished products (EMA/CVMP/QWP/709423/2022) should be utilised.

If the quality characteristics (e.g. physical characteristics, impurity profile) of the active substance are changed in a way that may impact the stability of the finished product, additional six months stability data from at least two batches of finished product, of at least pilot scale, under long term and accelerated* conditions, are recommended.

6.2. (F.I.a.1.b) Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. certificate of suitability is part of the approved dossier: The proposed manufacturer 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

In relation to stability data of the active substance, the recommendations given in the Guideline on stability testing of existing active substances and related finished products (EMA/CVMP/QWP/709423/2022) should be utilised.

If the quality characteristics (e.g. physical characteristics, impurity profile) of the active substance are changed in a way that may impact the stability of the finished product, additional six months stability data from at least two batches of finished product, of at least pilot scale, under long term and accelerated* testing conditions, are recommended.

6.3. (F.I.a.1.e) Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. certificate of suitability is part of the approved dossier: Introduction of a new manufacturer of the active substance that is not supported by an ASMF and requires significant update to the relevant active substance section of the dossier

In relation to stability data of the active substance, the recommendations given in the Guideline on stability testing of existing active substances and related finished products (EMA/CVMP/QWP/709423/2022) should be utilised.

If the quality characteristics (e.g. physical characteristics, impurity profile) of the active substance are changed in a way that may impact the stability of the finished product, additional six months of stability data from at least two batches of finished product, of at least pilot scale, under long term and accelerated* testing conditions, are recommended.

6.4. (F.I.a.2.a) Changes in the manufacturing process of the active substance: Substantial changes to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal 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 (e.g. physical characteristics, impurity profile) of the active substance are changed in a way that may impact the stability of the finished product, additional six months of stability data from at least two batches of finished product, of at least pilot scale, under long term and accelerated* testing conditions, are recommended.

6.5. (F.I.a.2.c) Changes in the manufacturing process of the active substance: The change relates to a herbal medicinal product and there is a change to any of the following: geographical source, manufacturing route or production

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* term 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 six months of stability data from at least two batches of finished product, of at least pilot scale, under long term and accelerated* testing conditions, are recommended.

6.6. (F.I.c.1.a) Change in immediate packaging of the active substance: Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological 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 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.

6.7. (F.I.f.1) Substantial changes in the updated version of the ASMF or the active substance part of the dossier

Depending on the scope of the changes and when the stability of the active substance is concerned, stability data should be provided following the same principles described for the relevant changes under code F.I.

6.8. (F.II.a.3.b.1) 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.

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

6.9. (F.II.a.4.a) Change in coating weight of oral dosage forms or change in weight of capsule shells: Gastro-resistant, modified or prolonged release pharmaceutical forms where the coating 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 the three batches should be at least pilot scale; the third batch may be smaller.

6.10. (F.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 the three batches should be at least pilot scale; the third batch may be smaller.

6.11. (F.II.b.1.a) Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product: Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products, or for pharmaceutical forms manufactured by complex 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, under 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, under long term and accelerated* stability testing conditions, on at least three primary batches, are recommended. Two of the three batches should be at least pilot scale; the third batch may be smaller.

6.12. (F.II.b.3.b) Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product: Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal 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, under 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, under long term and accelerated* stability testing conditions, on at least three primary batches, are recommended. Two of the three batches should be at least pilot scale; the third batch may be smaller.

6.13. (F.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 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, under 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, under long term and accelerated* stability testing conditions, on at least three primary batches, are recommended. Two of the three batches should be at least pilot scale; the third batch may be smaller.

6.14. (F.II.b.3.e) Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product: introduction or increase in the 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, under 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, under long term and accelerated* stability testing conditions, on at least three primary batches, are recommended. Two of the three batches should be at least pilot scale; the third batch may be smaller.

6.15. (F.II.b.3.h) Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product: Change in the holding time of an intermediate or bulk product (if applicable)

In variations to the holding time of an intermediate or bulk product, the change should be supported by appropriate stability data following the requirements of the Guideline on manufacture of the veterinary finished dosage form (EMA/CVMP/QWP/798401/2015), section 4.3.

6.16. (F.II.b.4.b) Change in the batch size (including batch size ranges) of the finished product: The change relates to all other pharmaceutical forms manufactured by 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, under 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, under long term and accelerated* stability testing conditions, on at least three primary batches, are recommended. Two of the three batches should be at least pilot scale; the third batch may be smaller.

6.17. (F.II.e.1.a.2) Change in immediate packaging of the finished product: Qualitative and quantitative composition: Sterile medicinal products and biological/immunological medicinal 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 the three batches should be at least pilot scale; the third batch may be smaller.

6.18. (F.II.e.1.a.3) Change in immediate packaging of the finished product: Qualitative and quantitative composition: 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 the three batches should be at least pilot scale; the third batch may be smaller.

6.19. (F.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 medicinal products and biological/immunological medicinal 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 the three batches should be at least pilot scale; the third batch may be smaller.

6.20. (F.II.e.4.a) Change in shape or dimensions of the container or closure (immediate packaging): The change in shape or dimensions concerns a fundamental part of the packaging material, which may have a significant impact on the delivery, use, safety or stability of the finished product

In variations to the immediate packaging of the finished product, which may have a significant impact of the stability 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:

- 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, under 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, under long term and accelerated* stability testing conditions, on at least three primary batches, are recommended. Two of the three batches should be at least pilot scale; the third batch may be smaller.

6.21. (F.II.e.5.b) Change in pack size of the finished product: Change in fill weight/fill volume of sterile multidose (or single-dose) parenteral medicinal product, including biological/immunological medicinal products

(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 the three batches should be at least pilot scale; the third batch may be smaller.

6.22. (I.I.1.a) Changes to the active substance(s): Replacement of a chemical active substance by a different salt/ester/complex/derivative, with the same therapeutic moiety, where the efficacy/safety characteristics are not significantly different

In case of change to the active substance concerning replacement of a chemical active substance by a different salt, ester, complex or derivative with the same therapeutic moiety, the long-term and accelerated* stability data should be presented for the active substance and for the related finished product in accordance with the Guideline on stability testing of existing active substances and related finished products (EMA/CVMP/QWP/709423/2022).

6.23. (I.I.1.b) Changes to the active substance(s): Replacement by a different isomer, a different mixture of isomers, of a mixture by an isolated isomer (e.g. racemate by a single enantiomer), where the efficacy/safety characteristics are not significantly different

In case of change to the active substance concerning replacement by a different isomer, a different mixture of isomers or of a mixture by an isolated isomer, the long-term and accelerated* stability data should be presented for the active substance and for the related finished product in accordance with the Guideline on stability testing of existing active substances and related finished products (EMA/CVMP/QWP/709423/2022).

6.24. (I.I.1.f) Changes to the active substance(s): Change to the extraction solvent or the ratio of herbal drug to herbal drug preparation where the efficacy/safety characteristics are not significantly different

In case of change to the active substance concerning changes to the extraction solvent or the ratio of herbal drug to herbal drug preparation, the long-term and accelerated* stability data should be presented for the active substance and for the related finished product in accordance with the Guideline on quality of herbal medicinal products/traditional herbal medicinal products (EMA/HMPC/CHMP/CVMP/201116/2005).

6.25. (I.II.1.c) Changes to strength, pharmaceutical form and route of administration: Change or addition of a new strength/potency

In case of change or addition of a new strength/potency for veterinary medicinal products, long-term and accelerated* stability data product should be presented on the finished product in accordance with the Guideline on stability testing of existing active substances and related finished products (EMA/CVMP/QWP/709423/2022).

6.26. (I.II.1.d) Changes to strength, pharmaceutical form and route of administration: Change or addition of a new pharmaceutical form

In case of change or addition of a new pharmaceutical form of veterinary medicinal products, long-term and accelerated* stability data should be presented on the finished product in accordance with the Guideline on stability testing of existing active substances and related finished products (EMA/CVMP/QWP/709423/2022).

7. Commitment batches

For variations not requiring assessment and for certain variations requiring assessment, where recommended documentation is listed in the classification guidance (typically VRA-R), that require the generation of stability data on the finished product, adequate follow up studies on commitment batches are necessary.

For variations requiring assessment under codes F, where recommended documentation is not listed in the classification guidance (typically VRA-S), 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.

For variations requiring assessment under codes I, adequate follow up studies on commitment batches are necessary as described in the Guideline on Stability Testing of Existing Active Substances and Related Finished Products (EMA/CVMP/QWP/709423/2022), section 2.2.8.

References

- Commission Implementing Regulation (EU) 2021/17 establishing a list of variations not requiring assessment
- Guidance on the details of the classification of variations requiring assessment (EMA/CMDv/7381/2021)
- Guideline on Stability Testing of Existing Active Substances and Related Finished Products (EMA/CVMP/QWP/709423/2022)
- Guideline on Stability Testing of New Veterinary Drug Substances and Medicinal Products (CVMP/VICH/899/99-VICH GL3)
- Bracketing and matrixing designs for stability testing of new veterinary drug substances and medicinal products (EMEA/CVMP/VICH/581467/2007-VICH GL45)
- Guideline on Statistical Evaluation of Stability Data (EMA/CVMP/VICH/858875/2011-VICH GL51)

- Note for guidance on quality of herbal medicinal products / traditional herbal medicinal products (EMA/HMPC/CHMP/CVMP/201116/2005)
- Note for guidance 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)

*according to VICH 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

Variations under codes F:

Where the data submitted, long term 25 °C/ 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 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, 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 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 CVMP/VICH Guideline on Statistical Evaluation of Stability Data.

Variations under codes I:

In case of extrapolation of the retest period of the active substance or of the shelf-life of the finished product beyond available long-term stability data, the principles described in the Guideline on Stability Testing of Existing Active Substances and Related Finished Products (EMA/CVMP/QWP/709423/2022) or the VICH guideline on statistical evaluation of stability data (VICH GL51) should be followed.