7 November 2024
EMA/CVMP/QWP/416589/2024
Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on 'Guideline on stability testing for applications for variations to a marketing authorisation for veterinary medicinal products' (EMA/CVMP/QWP/515653/2023)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Access VetMed
2	AnimalhealthEurope

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1. General comments – overview

Stakeholder no.	General comment	Outcome (if applicable)
1	Access VetMed do appreciate the opportunity for our Members being able to review and comment on this specific draft guideline. Please refer to the next sections for some specific comments/remarks to the proposed text. Clear and concise definitions for terms such as "conventional", "critical", "complex" do not seem to be included in the "Guideline on Process Validation for finished products". Therefore, it would be very much appreciated if those are included in this amended guideline, or alternatively, a detailed list of examples is included.	Not accepted. For conventional or critical dosage forms, there are already examples in the text of the guideline where relevant. For complex manufacturing process, an explanation is available on the EMA website section "Quality of medicines questions and answers: Part 1". Examples of complex processes are also available in the Annex II to the guideline on Process Validation (EMA/CHMP/CVMP/QWP/749073/2016)
2	AnimalhealthEurope would like to thank the CVMP for this guideline and is grateful for the opportunity to comment. Please find some comments below. Should you have further questions, AnimalhealthEurope is happy to provide any clarification needed. Several places in the GL Text referred to: "...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." Comment: The term "primary batch" and the wording "Two of the three batches should be at least pilot scale; the third batch may be smaller." seems to be repetition. It is proposed to delete the word "primary". Proposal: To avoid any confusion with the term "primary	Not accepted. A glossary is not necessary for this guideline. The terms "primary batch" and "commitment batch" are defined in the Glossary of the parent VICH GL3. The EU Guideline on Stability testing of existing active substances and related finished products (EMA/CVMP/QWP/709423/2022) also uses the same terminology. "Testing conditions" for stability are also described in the parent VICH GL3 as well as in the Guideline on stability testing of existing active substances and related finished products (EMA/CVMP/QWP/709423/2022).

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	batch", please add a glossary section and include a definition of this term. Several places in the GL Comment: For the better clarity, a glossary or a footnote could be added to explain "Commitment batches" (cf VICH GL 3) and "testing conditions".	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
122	1	**Comments:** In line with the vast majority of the text from Section 6, it is suggested that this guideline consistently states that these are recommendations and not requirements. **Proposed change:** "This guideline provides guidance on the stability data recommended to be generated in order to support a variation to a marketing authorisation for veterinary medicinal products."	Not accepted. The proposal for "Executive summary" would not be in accordance with the section 5 of this guideline where VNRAs are addressed. For VNRAs, the set of data are defined and not considered recommendations.
132-133	1	**Comments**: Access VetMed consider that in addition to the quality by design concept, other alternative approaches should be herein mentioned. **Proposed change:** "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, product/process know-how obtained after authorisation, GMP on-going stability studies, comparative stress testing of critical test parameters, correlation, extrapolation)."	Not accepted. There is no need to include more detailed list of examples. Quality by design is mentioned as a specific example as it is related to the enhanced development approach. Other justified alternatives related to traditional approach are allowed on case-by-case basis.
154-156	2	**Comments**: Text referred to: "…e.g. if outside specification or potentially outside specification." Comment: In GMP	Not accepted.

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		Chapter 8 on Quality Defects it is stated that "competent authorities should be informed in a timely manner in case of a confirmed quality defect". In line with what we do in accordance with GMP for batches in OGS programs, we propose that we only connect with regulatory bodies once we have a confirmed outside specification result in the stability studies for variations. This could also be emphasized in line 537. See below.	The referred lines do not relate to GMP ongoing stability programs but to formal stability studies.
170-174	2	**Comments**: Text referred to: "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), respect" Comment: It is proposed to clarify the expectation regarding Commitment Batches as follows for better clarity. **Proposed change:** Proposal: Please add a reference to section 7 on Commitment batches: "When stability data are required, the choice of test conditions, defined in this guideline refers to	Not accepted. The lines relate to the choice of the test conditions. There is no need to specifically refer to the section "7. Commitment batches".

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		• 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), respect. Whenever the above guidelines are being referred to, the reader should follow the requirements for Commitment Batches as described in section 7 of the present guideline"	
175-177	1	**Comments:** Access VetMed propose to specify the use of Bracketing/Matrixing approach in those examples where stability studies on two lots are recommended/required. **Proposed change:** 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. For products available in several strengths, it is noted that for variations requiring assessment where stability studies on at least two batches are recommended/required, the concept of bracketing and matrixing on two batches per strength may be also applied (as VICH GL45 guideline only provides	Not accepted. The general reference to VICH GL45 is deemed sufficient for the purpose of this guideline.

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		examples of bracketing and matrixing on three batches per strength).	
213	1	**Comments:** In order to streamline the approval process of a VRA without impacting the quality of the VMP, Access VetMed propose to include an additional wording to this section. **Proposed change:** Add after Line 213: "In those cases where 6-month stability data is required, the variation could be submitted if satisfactory 3-month accelerated stability data is at the disposition of the Applicant, and 6-month stability data is presented before the end of the Variation assessment / procedure is completed.	Not accepted. The given proposal should not be a standard practice. In order to streamline approval of VRAs, the expected stability data should already be available at the time of the initial variation submission.
220-221	2	**Comments:** Text referred to: "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." Comment: It is our understanding that stability data should be provided only in case a retest period is claimed. **Proposed change:** Proposal: Please amend the text to read: "In case of an introduction of a manufacturer of the active substance that is supported by an ASMF stability data	Not accepted. It is agreed that there is an option not to establish retest period but to test the active substance prior to the manufacture of the related finished product. However, this concept is not new as it already existed before the new veterinary legislation was implemented, for example, for substances described in the Ph. Eur. monographs and for MUMS products). In addition, the next lines 222-224 refer to the Guideline on Stability Testing: Stability testing of existing active substances and related finished products (EMA/CVMP/QWP/709423/2022) where this aspect is described in section 2.1.1.

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		should be included in the applicant's part of the ASMF in case a retest period is claimed."	No change is thus considered necessary.
225-228	1	**Comments:** For finished products, the stability requirements are the same independently of the API being supported with an ASMF or not. This seems not fully consistent. For APIs with a CEP, no stability data for the finished product is required. However, for an API supported with an ASMF, 6 month stability data on two batches of the finished product is recommended (identical to APIs not supported with an ASMF). Access VetMed would very much welcome less strict requirements for APIs supported with an ASMF. **Proposed change:** Change Lines 225-228 to read: "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 three months stability data from at least one batch of finished product, of at least pilot scale, under long term and accelerated conditions, are recommended, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).	Not accepted. In regard to a new ASMF, the additional 6 months stability data on the related finished product are recommended only in the case where the quality characteristics of the active substance are changed in a way that may impact the stability of the finished product (lines 225-226). For changes to CEPs, the conditions for respective VNRA would not be fulfilled in case the quality characteristics are changed in such a way. Consequently, it should be submitted as a VRA "z"-variation and the same principles as for a new ASMF should apply.

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227, 244, 258, 276, 315, 351, 369, 385, 400	1	**Comments:** Access VetMed consider the changes covered under these lines as 'minor'. Therefore, it is proposed to introduce an option to submit the stability of at least one batch of the final product of at least pilot size under VICH conditions, and a commitment to place at least one additional GMP batch (Registered batch size) on stability, and immediately inform the relevant Competent Authorities in the event of obtaining an OOS result. **Proposed change:** Adjust the text in the mentioned lines as suggested in the 'Comments and Rationale' column.	Not accepted. Results of stability studies on one pilot batch only is not considered sufficient for such changes.
295-297	2	**Comments:** Text referred to: "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" Comment: The title could bring confusion in that it would apply on substances that are both sterile and non-frozen. The sentence might be read as only applicable to changes in immediate packaging of solely to biological/immunological active substances. However, it's important to clarify that these substances are explicitly outside the scope of the current guideline (see lines 141-142). So, in order to clarify this, we would propose modifying the title. In	Not accepted. The title of the change should be quoted exactly as in the variation classification guideline.

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		parallel, we are also proposing to align the title for the F.I.c.1.a in EMA/CMDv/7381/2021: Change in immediate packaging of the active substance: "Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological active substances" **Proposed change:** Proposal: Please modify to read: "6.6. (F.I.c.1.a) Change in immediate packaging of the active substance: Qualitative and/or quantitative composition for sterile active substance or non-frozen biological/immunological active substances" or even to read "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"	
417-426	1	**Comments:** Although it is acknowledged that the provision of stability data in this section is only 'recommended', Access VetMed respectfully consider that these requirements are excessively strict in some circumstances. E.g., Solutions for injection that are sterilised by filtration may be categorised by EU Competent Authorities as a complex manufacturing process, as they do not use terminal sterilisation, and despite the product is ultimately a true solution where the compounding process could be quite simple. As a matter of fact, for oral solutions, the Variation / change can be addressed with a Variation Not	Not accepted. According to the lines 417-426, the stability studies are required only in cases when quality characteristics may be compromised. In case the quality characteristics are not compromised by the change (even for complex processes), no stability data are required. When the stability data are needed, the proposal to test only one pilot batch with results on 3 months is not sufficient.

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		Requiring Scientific Assessment. In our opinion, a batch size increase only requiring process changes related to changes in equipment should not require 6-month comparative stability data. There is no reason to treat the stability requirements for these solutions differently than for other solutions, as far as relevant and valid Filter validation studies have been presented for the new proposed batch size. **Proposed change:** Replace lines 420-422 to read: "For conventional dosage forms manufactured by a complex manufacturing process and when the active substance is known to be stable, comparative stability data, 3 months in duration, under long term testing conditions, on at least one batch of at least pilot scale, is recommended, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).	
445	2	**Comments:** Comment: "comparative stability data" might benefit from more detailed description. E.g. Does the same batch need to be filled in the current and the proposed packaging or an older stability study with the current packaging material can be compared with	Not accepted. The guideline should not include such specific details or examples.

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		a recent stability study with the proposed packaging material?	
453-454	1	**Comments:** A matrixing and bracketing approach, according to EMEA/CVMP/VICH/581467/2007-VICH GL45, is acceptable as outlined in section 4 'General requirements' of this proposed guideline. For clarity and emphasis, Access VetMed would appreciate if that reference is also included in this section. **Proposed change:** "In case of a change to the immediate packaging of the finished product the following approach may be considered as acceptable (including the use of an appropriate bracketing and matrixing approach, as applicable):"	Not accepted. The section "4. General requirements" should always be read together with each individual variation category.
480-481	1	**Comments:** Same comment as for Lines 453-454 **Proposed change:** "In case of such a change to the pack size of the finished product the following approach may be considered as acceptable (including the use of an appropriate bracketing and matrixing approach, as applicable) "	Not accepted. See above, lines 453-454.
527-530	2	**Comments:** Text referred to: "For variations not requiring assessment and for certain variations requiring	Not accepted.

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		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." **Proposed change:** Proposal: For better clarity, we propose to amend this § to read: "As stated in the classification guidance, mandatory finished product stability studies initiated on behalf of variations not requiring assessment and for certain variations requiring assessment (typically VRA-R), should continue through the end of the registered stability study protocol"	The proposed wording does not cover all scenarios of VNRA/VRA-R.
537	2	**Comments:** Text referred to: "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." Comment: In order to avoid any administrative burden for MAHs and authorities alike, we propose that we only connect with regulatory bodies once we have a confirmed (and not any) problem or outside specification result in the stability studies for variations. See also comment on lines 154 – 156. **Proposed change:**	Not accepted. All potential problems appearing within stability studies should be communicated to the authorities.

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		Proposal: Please modify the sentence to read: "…the authorities should be informed if any confirmed problems appear with the stability studies".	