23 October 2017
EMA/CVMP/QWP/502315/2017
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Draft Guideline on the chemistry of active substances (veterinary)' (EMA/CVMP/QWP/49477/2017)

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

Stakeholder no.	Name of organisation or individual
1	AnimalhealthEurope (IFAH-Europe)
2	European Group for Generic Veterinary Products (EGGVP)
3	APIC

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	AnimalhealthEurope welcome the opportunity to comment on the Guideline on the chemistry of active substances (veterinary). In the introduction of the draft guideline it is described that requirements for veterinary medicinal products (VMP) are different from human products which is very much appreciated however it would be considered beneficial to define in more detail the specific requirements for VMPs. Therefore AnimalhealthEurope would strongly encourage EMA to bring more clarity to the text on this aspect. AnimalhealthEurope would like to extend this request to other documents as a general rule.	Noted. Differences in requirements for VMPs as interpreted by IFAH Europe are not outlined in the introduction. No need to define specific requirements for VMP, more in detail in the introduction.
2	The Quality Working Group of the EGGVP has reviewed the contents of this new Reflection paper from the EMA. While the initiative is welcome by the Group, there are no general of specific comments to be made on the text.	Noted.
3	In this document there are many references to e.g. VICH and CVMP guidelines which were written for NEW active substances. In our opinion the corresponding paragraphs should thus only be taken into account for new active substances and NOT for existing ones.	Noted. It is the clear intention to publish a guideline for new as well as for existing active substances (see also the concept paper). There are currently two approved guidelines on the subject; EMEA/CVMP/541/03/Final guideline on the chemistry of new active substances and 3AQ5A guideline on chemistry of the active substance which have to be combined in one single guideline. In the Scope (line 18/19) it is already stated: “The differences in requirements for new or existing active substances are clarified in the relevant paragraphs of the guideline where applicable.”

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
70-73	1	**Comments**: Manufacturer(s): the draft GL foresees that the name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided. It is not clear to which extent/level of detail should contractors be mentioned. **Proposed change**: Please clarify.	Not accepted. There is no intention to increase the requirements on applicants from the changes to this GL. This wording (including the term "contractor") was copied from the existing CVMP GL on the chemistry of new active substances.
74-81	1	**Comments**: Description of Manufacturing Process and Process Controls: Shall the description of the process for existing APIs be as detailed as for new ones? (see also lines 223-226 – 4.2.6. manufacturing process development and lines 308ff. Impurities) **Proposed Change**: Please clarify	Not accepted. In principle, the description of process for existing APIs should be the same as for new APIs.
89-95	1	**Comments**: In line 92, reference is made to a representative production scale batch. This is not applicable for submission of development APIs, not yet approved. At this stage the commercial scale production may not have been performed at all. **Proposed change**: Please amend the text: "…~~used in a current representative production scale batch~~" to read "…used in a batch representative to production scale."	Not accepted. There should be no difference if compared to the corresponding CHMP GL as this could cause confusion.
101-104	1	**Comments**: The following sentence "However, if alternative steps or solvents are proposed they should be justified by providing sufficient evidence that the	Not accepted. There should be no difference if compared to the corresponding CHMP GL as this could cause confusion.

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		final quality of the material (i.e.: active substance or isolated intermediate) obtained remains unchanged if the submission of data is via a CEP and/or an ASMF" might need to be rephrased for clarity reasons. **Proposed change**: Please modify the sentence to read: "However, in case the information for an active substance or intermediate is provided via a CEP and/or an ASMF, and alternative process steps or solvents are proposed to be used, only the proposed alternative process steps or solvents should be justified. For justification, sufficient evidence should be provided that the final quality of the active substance or isolated intermediate obtained by introducing the alternative process steps or solvents remains unchanged compared to the quality described in the CEP or ASMF".	
129-132	1	**Comments**: Reference to a reflection paper seems to be not adequate as this is used to communicate the current status of discussions or to invite comment on selected area of product development. It can provide a framework for discussion or clarification particularly in areas where scientific knowledge is fast evolving or experience is limited. A reflection paper does not provide scientific, technical or regulatory guidance." **Proposed change**: Please amend the sentence to read: "The requirements of ICH Q11 (Ref 4) in relation to the selection of starting materials are relevant to all active substances, regardless of the type of development approach. ~~Reflection paper on the requirements for selection and justification of starting~~	Accepted. Reference to the reflection paper was deleted.

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		~~materials for the manufacture of chemical active substances (Ref 9) should also be consulted~~.	
240-244	1	**Comments**: It is mentioned that the evidence of structure should be related to material to be used in marketed product. This is not quite clear, or misleading. The first part of the section should be sufficient as guidance. **Proposed change**: Please delete the last sentence: "~~It is important… complex molecular structures~~."	Not accepted. Especially for highly complex molecular structures (e.g. large peptides) it is important to have evidence of the structure (e.g. in case of biosimilars).
256, 261-262	1	**Comments**: Mass spectrometry is mentioned twice, once can be omitted **Proposed change**: Please delete sentences 261-262	Not accepted. Line 256 comprises the complete mass spectra including fragmentation reactions and analysis of these fragments whereas line 261-262 relates to the relative molecular mass. No change.
259	1	**Comment**: It is not clear what is meant with "diagnostic of the structure" **Proposed change**: Please modify the sentence to read: "Characteristic chemical reactions which scientifically only lead to the structure of the molecule."	Not accepted. The meaning of the wording is clear and understandable. There should be no difference in terminology if compared to the corresponding CHMP GL as this could cause confusion.
281	1	**Comments**: Hot-stage microscopy is not commonly used **Proposed change**: Please delete "~~(including hot-stage microscopy)~~"	Not accepted. Only examples are given here. Method becomes more and more important.
282	1	**Comments**: Solid state IR and NIRS are not commonly used **Proposed change**: It should read solid state IR **or** NIRs	Partly accepted. Change to "Solid state IR **and/or** NIRS".
309-310	1	**Comments**: elemental impurities: Without an additional explanation, "Elemental	Not accepted. With the implementation of supplement 9.3 of the European

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		Impurities" are widely understood as the requirements as defined in the *ICH guideline Q3D on elemental impurities* which is not valid for Veterinary submissions. The requirements for substances used for Veterinary Medicinal products are being discussed in the frame of the European Pharmacopeia and the final wording of the relevant chapters is still not published. Additionally, IFAH Europe has requested to have a more specific Veterinary guidance on the expectations of the assessors to fulfil this new requirement. From discussions at the QWP, it is the understanding for IFAH Europe that the main concerns of the Veterinary Quality Assessors are the discussions of the intentionally added elements, such catalysts (and reagents), used during the last step of the synthesis and their carry over. In order to avoid that this guideline includes additional requirements for the Veterinary Industry, it is suggested to limit the discussion to the catalysts and reagents used during the last step of the synthesis or their carry overs. Further developments of the monograph are already covered by lines 381 and "The requirements of the general monograph of the European Pharmacopoeia *Substances for Pharmaceutical Use* (2034) should be met, where applicable" **Proposed change**: Please amend this sentence to read: "Information on impurities and their carry-overs should be provided. This includes related substances, and residual solvents~~, elemental impurities, reagents and those derived from reagents~~. For elemental	Pharmacopoeia (January 2018) the Ph. Eur. General Monograph *Substances for Pharmaceutical Use* requires that elemental impurities are considered in a risk assessment (regardless whether for human or for veterinary use) and the Ph. Eur. General Monograph *Pharmaceutical Preparations* requires elemental impurities to be controlled based on a risk assessment for products outside the scope of Ph. Eur. Chapter 5.20.

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		impurities derived from catalysts intentionally added in the last synthesis step and carry overs of elemental impurities or reagents to the last synthesis step, their identity is known and strategies for controlling them are established by using the principles of risk management.”	
397-398	1	**Comments**: It is understood that the secondary packaging materials e.g. fibre drums, should be described. From the current text, it could be understood that also identification and specification for secondary packaging are required. This would result in additional details to the dossier that are not relevant and would cause additional administrative burden and potentially variations. **Proposed change**: Please amend the sentence to read: “A brief description of the storage container closure system(s), including ~~specifications with suitable identity test(s) and~~ details of materials of construction should be provided. Specifications and suitable identity tests should be provided for the primary packaging material”.	Not accepted. There is no intention to increase the requirements on applicants from the changes to this GL. A similar sentence is already stated in the existing CVMP GL on the chemistry of new active substances. The container closure system is the sum of packaging components that together contain and protect the active substance. This includes immediate packaging components and secondary packaging components, if the latter are intended to provide additional protection. Specification(s) with suitable identity test(s) are essential.