29 November 2017
EMA/CVMP/QWP/759110/2017
Veterinary Medicines Division

Overview of comments received on 'draft guideline on implementation of risk assessment requirements to control elemental impurities in veterinary medicinal products' (EMA/CVMP/QWP/631010/2017)

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

Stakeholder no.	Name of organisation or individual
1	Elanco
2	Pharmacosmos A/S
3	AnimalhealthEurope
4	APIC (Active Pharmaceutical Ingredients Committee)
5	Dada Consultancy BV

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Elanco is extremely appreciative of the phased-in approach drafted by the CVMP. This guidance will alleviate stress across the animal health industry, as it was difficult (at best) to apply the human health PDE-risk based approach to veterinary products. Elanco would like to provide feedback on this draft in hopes that the approach is clarified in certain areas and to ensure all aspects of this topic are taken into account. We also commit to providing feedback on the "further guidance" communicated as being "elaborated and published in due course". Elanco has concerns surrounding the further guidance, in general. Will this guidance take into account the differences between the products in our industry, such as food animal products versus companion animal products? Will routes of administration still be considered, as is currently described in ICH Q3D? Is it possible to develop PDE limits for various species or will the elaborated risk assessment focus more on understanding the manufacturing process from a holistic viewpoint? These concerns are only a high-level example of our line of thinking. Once this guidance is released, Elanco is committed to providing feedback. We kindly request that the further guidance is released in draft form with a minimum of two months to complete our internal reviews and assess impact across our organization and various product lines.	Acknowledged that the consultation period for this guidance is exceptionally short.
2	Pharmacosmos A/S wishes to propose that this guideline addresses the use of human PDE data, in establishing PDEs for class I elemental impurities in veterinary medicinal products. A comparable approach is applied in VICH GL 18, with human PDEs used as the basis for	Noted. However, it is not considered appropriate to comment on or pre-empt what information will be provided in future guidance.

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	calculating residual solvent limits in veterinary medicinal products. Requiring human PDEs for class I elemental impurities, appropriately dose and weight adjusted for the animal species, should be the standard advocated for veterinary medicinal product risk assessments. Any exceptions should be specifically justified in the specific risk assessments. Exceptions should not be considered as justifiable for veterinary medicinal products intended for juvenile animal species or for food producing animals.	
3	We welcome the opportunity to review and comment on the draft guidance. AnimalhealthEurope highly appreciates that CVMP has recognised that trying to apply the human health requirements of a risk assessment, specifically the permitted daily exposure (PDE) approach, to veterinary products is very difficult if not impossible and also appreciates that CVMP is proposing a phased-in approach. However, there are two major areas of concern that we would like to detail in this paper. First it seems there is a major incoherence in this document because although it is said at lines 14 – 16 that there is no regulatory action expected so far given that guidance is not available yet, risk assessment for new products registration is requested by January 2018. As the final guidance on risk assessment has not yet been released for consultation, we would request postponing this specific requirement until such guidance is effective. Current control strategies likely utilise the compendia requirements of heavy metals. We would request a clarification in lines 14-16 that not only states regulatory action is not expected at this time, but additionally that current control strategies are acceptable until risk assessments are	Noted. Lines 14-15 to be amended to state *Regulatory action is not expected at this time i.e. routine submission of risk assessments via variations, or otherwise, is not envisaged. Current control strategies are considered acceptable until a risk assessment is required in line with the phased implementation outlined overleaf.* With respect to the proposed change to the approach it is considered that the issues mentioned with respect to route of administration, accumulation along the food chain etc. are issues that are more appropriately considered in the context of additional guidance rather than this initial proposal for a phased approach. In the reference to the QWP interested parties meeting in June 2017, there appears to be some misunderstanding. At that meeting it was agreed that provision of mock risk assessments by industry representatives would be useful to regulators to feed into the elaboration of future guidance. QWP remain open to submission of these documents,

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	required to be executed. Secondly, we have major concerns around the proposed timelines included in the decision tree. We believe that in general, these timelines should be the result of a risk - based approach for the evaluation of metal impurities in veterinary medicinal products, according to the risk presented to humans. The focus should be on those impurities prone to cumulate along the food chain (e.g. for elements like Hg, Cd, As, Pb etc.). The guideline must therefore distinguish between: - products for food animals oral >< companion animals oral, - products for food animals topical with systemic effect ><products for companion animals topical with systemic effect, - ectoparasiticides with pure topical external effect. Please note that it has to be questioned if this exercise has to be performed for ectoparasiticides at all, given that the regulatory environment is different than for the other products (e. g. no GMP certificate for the API, lower standards for excipient quality etc.). In this context, the benefit expected from risk assessment on this type of products would be very limited or even non-existent. Regarding legacy products, AnimalhealthEurope would suggest considering three scenarios or re-wording the two current scenarios (3a and 3b) in the decision tree. In our opinion, there are three different types of products with an increasing amount of complexity in a potential risk assessment: those with known sources of elemental impurities (i.e. catalyst), those with potential sources of	however, none have been provided to date.

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	elemental impurities (i.e. contributions from a mined excipient), and those with unknown levels of elemental impurities (currently listed as all others). Our interpretation of the decision tree is that products with potential and/or unknown sources of elemental impurities fall under the "All products" category. Should the current categories remain the same, we would request additional verbiage clarifying what is included in "All products". Based on the reflections above and taking into consideration the specificities of the Animal Health businesses, we would like to propose alternative timelines that we have detailed in the "specific comments" area below. We look forward to partnering with the CVMP in further discussions on timelines. As proposed and accepted during the Quality WP with interested parties meeting held last June 2017, AnimalhealthEurope volunteered to prepare a document proposing what would be the principles of the risk assessment for the veterinary products.	
4	In the absence of PDE applicable to animal species, it seems unrealistic to set deadline for implementation for new MA with New Active Substance to January 2018, which is 6 weeks from now. We suggest setting the deadline to January 2019 or later.	Noted. However, the European Pharmacopoeia monographs become effective on 1st January 2018 and are legally binding. Therefore in the absence of agreement of a phased approach, compliance will be required for all products from 1st January 2018 onwards.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 5–8	5	**Comment**: It is indicated that: "In the case of veterinary medicinal products, the scientific principles on which risk assessment/risk management should be based have not yet been elaborated as the permitted daily exposure (PDE) based approach detailed in General Chapter 5.20 and in ICH Q3D cannot be easily applied to veterinary products." It is recommended to distinguish between food-producing animals and companion animals. As long as no guidance has been elaborated for a suitable approach for risk assessment for veterinary medicinal products, it is suggested that for food-producing animals, a risk assessment should at least consider the potential risk to humans that consume food derived from these animals. Since the risk of contamination with elemental impurities is very low, it is also suggested to postpone the risk assessment for veterinary products for companion animals until specific guidance has been established.	Not accepted. Distinguishing between food-producing animals and companion animals is considered more appropriately dealt with in the guidance to be developed rather than this initial proposal for a phased approach.
Lines 9-11/General	1	**Comments:** By not knowing when the "appropriate approach for a risk assessment for a veterinary medicinal product" will be released, it becomes extremely difficult to comment on the exact dates	Accepted that expectations from a regulatory perspective are currently unclear. However, the European Pharmacopoeia monographs become effective on 1st January 2018 and are legally binding.

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		proposed in the draft's decision tree. In other words, how can we know if we are able to meet a proposed implementation date if we do not have the full expectations from a regulatory perspective? This level of uncertainty only allows Elanco to provide comments on the implied timelines for the different scenarios provided in the decision tree.	Therefore in the absence of agreement of a phased approach, compliance will be required for all products from 1st January onwards.
Lines 9-10	3	**Comment:** A harmonised guidance between EU, Japan and US would be preferable.	Not accepted. The issue arises as a result of changes to the European Pharmacopoeia monographs which are only legally binding within the EU.
Lines 9–13	5	**Comment**: It is indicated that: "In order to allow time for regulators to elaborate guidance on the appropriate approach for a risk assessment for a veterinary medicinal product, the CVMP has adopted the following measured approach to the implementation of the monograph to existing veterinary products. The phased-in implementation of the risk assessment of elemental impurities in veterinary medicinal products is to be in accordance with the decision tree indicated in this document." According to the decision tree, a risk assessment should be conducted by January 2018 for new marketing authorisations with new active substances. Since it is expected that no new guidance will be available by then, it is considered important to clearly define the term "new active substance" within the	Accepted. Clarification on the definition of new active substance has been included in the guidance and corresponds to the definition in VICH GL39 "Test procedures and acceptance Criteria for new veterinary drug Substances and new medicinal products: Chemical substances": The designated therapeutic moiety, which has not previously been registered in a region or Member State for use in a veterinary medicine (also referred to as a new molecular entity or new chemical entity). It may be a complex, simple ester, or salt of a previously approved drug substance.

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		context of this draft guideline. Different definitions of the terms “new active substance” or “new drug substance” are given in various veterinary guidelines: • Designated therapeutic moiety, which has not previously been registered in a region or member state (also referred to as a new molecular entity or new chemical entity). It may be a complex, simple ester, or salt of a previously approved drug substance (EMEA/CVMP/134/02 Rev 3/Corr). • Designated therapeutic moiety that has not been previously registered in a region or member state in a veterinary medicinal product (also referred to as a new molecular entity or new chemical entity). It can be a complex, simple ester, or salt of a previously approved drug substance (EMEA/CVMP/VICH/837/99-Rev.1 (= VICH GL10) and EMEA/CVMP/VICH/838/99-Rev.1 (= VICH GL11)). • Active substance, used for the first time in a medicinal product either for human or veterinary use (EMEA/CVMP/1069/02) • Active substance (new chemical entity), used for the first time in a veterinary medicinal product (EMEA/CVMP/541/03/Final) • Active pharmaceutical substance not previously contained in any medicinal product registered with	

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		the national or regional authority concerned. A new salt, ester, or noncovalent bond derivative of an approved drug substance is considered a new molecular entity for the purpose of stability testing under this guidance. (CVMP/VICH/899/99 Rev. 1 (= VICH GL3)).	
Lines 14-16	1	**Comments:** Many of Elanco's products have legacy control strategies that currently utilize the heavy metals test based on the compendia testing requirements and specifications. **Proposed change:** In addition to stating "Regulatory action is not expected at this time…", we suggest a clarification or additional verbiage stating current control strategies will be sufficient until a risk assessment is completed or until regulatory action becomes required.	Partly accepted. The following text will be added. *Current control strategies are considered acceptable until a risk assessment is required in line with the phased implementation outlined overleaf.*
Lines 14 – 16 and Page 3: Decision tree (1)	3	**Comment: "***Regulatory action is not expected at this time and routine submission of risk assessments via variations, or otherwise, is not envisaged. Further guidance of expected regulatory actions will be elaborated and published in due course."* Re timelines for new MA with new Active Substance, the document suggests conducting a risk assessment by January 2018. AnimalhealthEurope strongly disagrees with this timing because as it is well said at lines 14 – 16, regulatory action is not expected as the guidance is not available yet and needs to be	Not accepted. A clear deadline must be established for compliance and establishing a timeframe based on publication of a future guidance is not considered appropriate. Note that in the absence of agreement of a phased approach, compliance will be required for all products from 1st January 2018 onwards.

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		developed. When can new guidance be expected? **Proposed change:** This date is not appropriate and should be changed. As the final guidance has not yet been released for consultation, we would request postponing this specific requirement until such guidance is effective. A transition period for the implementation should be allowed. This transition period may need to be longer if risk assessment process is complex (as indicated at line 8). Please consider that the human pharmaceutical sector had 36 months after publication of the guideline by ICH to implement the ICH Q3D requirements for existing products and 18 months for development products.	
Lines 15-16	1	**Comments:** The statement "further guidance…will be elaborated and published in due course", is both clarifying and arbitrary at the same time. Knowing that additional guidance is coming will be extremely helpful. However, the release of this guidance "in due course" adds a level of uncertainty. Elanco has been formalizing an internal strategy to address the elemental impurity topic for our products, utilizing a combination of risk-based principles from ICH Q9 and ICH Q3D, where applicable. The source of this strategy stems from a press release from the EDQM in 2015. Knowing we will have a full guidance available, while extremely helpful, could potentially cause further delays if/when it does not directly align with the	Accepted. Current proposal is that draft guidance be available by Q1 2019 although QWP will endeavour to make it available as soon as possible.

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		internally developed process. For this reason, we expect implementation efforts to be reactionary in nature to the release of this guidance. **Proposed change:** Provide an estimated timeline of the release of "further guidance" in draft form, so that we may approach implementation appropriately. We do not want to begin implementing something if it does not align with this "further guidance".	
Decision Tree (1 & 2)	1	**Comments:** For new submissions with new active substances, an implementation date of January 2018 seems very aggressive. Elanco expects it would take a minimum of 3 months to construct the necessary framework for these submissions once the final guidance becomes official. This timeline also assumes more of a holistic approach, which is not based on testing or meeting specifications. Should the requirements be more stringent than this, we would expect a minimum 6-12 months for testing development and validation activities. Overall, we suggest postponing this specific requirement until such a guidance is effective. We agree with the implied duration between scenario 1 and scenario 2 (1 year), but would request both scenario's be based off the effective date of the final guidance. **Proposed change:** As an example, let us assume the final guidance becomes effective in Q1 of 2018. We would suggest implementation dates of July 2018 for	Partly accepted. The issues around timing of guidance and implementation dates is acknowledged. Nevertheless it must be recognised that in the absences of a phased approach, compliance will be required for all products from 1st January 2018 onwards. It is proposed to amend the deadlines as detailed below: Scenario 1: Risk assessment required by January 2020. Scenario 2: Risk assessment required by January 2021.

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		Scenario 1 (New MA w/ new Active Substance) and July 2019 for Scenario 2 (New MA w/ existing Active Substance) when executing a holistic approach. Should the further guidance require testing development and validation activities, we would suggest implementation dates of January 2019 and January 2020 for Scenarios 1 and 2, respectively.	
Decision Tree (3)	1	**Comments:** Elanco currently recognizes three scenarios for our legacy products, with an increasing amount of complexity in the requirements for risk assessment. Categories: • Those with known sources of elemental impurities (i.e., due to use of a metal catalyst, or known contribution from container closure) • Those with known potential sources of elemental impurities (i.e., use of an excipient from a mined source) • Those with unknown levels of elemental impurities It is our interpretation that the last two categories are currently grouped within Scenario 3b – "All products". We request separating these products into the three categories described above, or including additional verbiage surrounding "all products". Additionally, we have some concerns for the timing suggested for legacy products, due to the complexity and size of our portfolio. Making the assumption that the formalized	Partly accepted. It is acknowledged that there are numerous ways in which products could be categorised with respect to risk and a decision tree applied to address this issue. The current proposal is not significantly different to that suggested. Bearing in mind that guidance will be available in Q1 2019, it is proposed to retain the existing categorisation of products and to amend the deadlines as detailed below: Scenario 3a: Risk assessment required by January 2021. Scenario 3b: Risk assessment required by January 2022. It is unclear what additional verbiage surrounding 'all products' would be required. All authorised veterinary medicinal products would be required to comply with the Ph. Eur. monographs by the last date stated in the decision tree.

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		guidance will be holistic in nature, we have generated a tentative suggestion for the timeline proposals. **Proposed change:** Keeping the same assumption as used before (effective final guidance in Q1 of 2018), we would suggest implementation dates as follows: • Products w/ known sources – July 2019 • Products w/ known potential sources – July 202 Products w/ unknown sources – July 2021	
Page 3: Decision tree (1, 2, 3, 3a and 3b)	3	**Comment:** The risk-based approach described in the "general comments" area above should help to focus on those products where the risk to have metal impurities contamination is higher and therefore potentially having a negative impact on product safety in that respect. **Proposed change:** Proposed timelines are: 1. Systemic products for food animal species: • For **new** applications, this should be done 18 months after the publication of the guideline • For **legacy products** → 36 months after publication of the guideline 2. For non-systemic products for food animal species: e.g. within 60 months	Not accepted. It is acknowledged that there are numerous ways in which products could be categorised with respect to risk and a decision tree applied to address this issue. Some changes to the timeframes are now proposed but the basis on which the current decision tree is based will be retained as it is considered simple and easy to implement, whilst allowing time for stakeholders to address the issue of elemental impurities in veterinary medicinal products.

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		3. It is considered advisable to first review the experiences gained before trying to apply arbitrary timelines to other products where already the risk is lower e.g. non-systemic activity of products for companion animals 4. Ectoparasiticides with pure topical external effect should be excluded from this exercise.	
Decision Tree (3a)	4	**Comment:** *'Products in which an elemental impurity is intentionally added e.g. catalyst/reagent at any stage of manufacture'*. This formulation is ambiguous. 'Any stage of manufacturing' is too broad. The consensus is that the notion of 'intentional addition' starts with the API starting materials, presence of EI due to use upstream is considered as contaminants. Wording should be aligned with ICH Q7 terminology. Proposed change (if any): *'Products in which an elemental impurity is intentionally added e.g. catalyst/reagent at any stage of manufacture after introduction of API starting materials.'*	Accepted. Wording has been changed as follows: Veterinary Medicinal Products in which an elemental impurity is intentionally added e.g. metal catalyst/reagent at any stage of manufacture after introduction of API starting materials.