EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 January 2020
EMA/CVMP/QWP/434956/2019
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on Reflection paper on risk management requirements for elemental impurities in veterinary medicinal products (EMA/CVMP/QWP/153641/2018)

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

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

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	AnimalhealthEurope very much welcomes having a specific GL for veterinary. However, we strongly recommend to modify the Chapter 4 – Risk Assessment and the Chapter 6 – Setting acceptable limits, to allow differentiation between animals for food production and companion animals and also have adapted PDE calculations to the actual animal species weights. We strongly believe that the risk level between animals for food production and companion animals is fundamentally different because: - Elemental impurities in VMP for food animals could cumulate across the food chain and could potentially cause toxicological effects in human beings. - On the other hand, elemental impurities in VMP for companion animals won't enter the food chain and therefore would only be potentially a risk, if the animal owner gets in direct contact with the VMP. Also, chapter 6- Setting acceptable limits, should allow calculation of the PDEs for any elemental impurity, according to the standard body weight of target species as proposed in the official Eudralex database (see specific comments below). Based on the outcome of the risk assessment with regard to the consumer risks, it would be desirable to have the opportunity to allow using human PDE values in cases where the risk assessment addresses a health risk for human beings, like in the case of VMP used in food animals. Only in cases where there is a concrete toxicological risk for the species in focus, a specific PDE should be required.	Elemental impurity could be a toxicological concern for any species. Differentiation between food and non food producing species is not accepted. This RP gives the possibility to propose value higher than the PDE if justified. Recalculation of the PDE based on the actual body weight of the target species is acceptable. The text has been amended accordingly.

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2	In relation to lines 201 & 202 of this reflection paper, we are in the opinion that as safety issues raised by elemental impurities in veterinary products may differ from human medicines, PDEs should be defined per animal species before a risk analysis can be applicable to veterinary products.	Noted. A guidance on principles of risk management applied to elemental impurity on veterinary medicines is considered required to fulfil the requirements of the Ph. Eur. monograph 2619, that now states that "*For pharmaceutical preparations outside the scope of general chapter 5.20, manufacturers of these products remain responsible for controlling the levels of elemental impurities using the principles of risk management*". The principles of the ICH Q3D are considered acceptable to ensure the quality and the safety of the medicinal product. This approach has been agreed by the CVMP in June 2018.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
59	1	Comment: While the title of the reflection paper makes it clear that only elemental impurities are covered, the scope does not clarify that elements intentionally added as (part of) active substances are excluded. Proposed change: Please include the following at the end of the sentence in line 59: "and elements that are intentionally included in the drug product for therapeutic benefit."	Accepted. The scope of the reflection paper has been amended in that sense.
109-110	1	Comment: Makes reference to ICH guideline Q3D for detailed information on risk assessment while it has been agreed that this guideline cannot easily be applied to veterinary medicines. Proposed change: Reference should be removed and details should be included.	Not accepted. The level of information from the ICH Q3D is considered sufficient. Also reference to specific sections of the ICH Q3D is given in this RP. The text remains unchanged.
130 - 145	1	Comment: This section imposes much higher requirements than the draft FDA GfI 255 which states for manufacturing equipment: "CVM considers the risk from manufacturing equipment to be low in most cases. Unless an unusual amount of equipment corrosion or wear is anticipated as a result of the manufacturing process, no further assessment is expected." In the spirit of international harmonization, it is proposed to adopt the draft FDA approach. Proposed change: Please replace lines 130 – 145 by "EMA considers the risk from manufacturing equipment to be low in most cases. Unless an	Not accepted. The scope of the reflection paper is veterinary medicinal products authorised or to be authorised in the EU. There is no intention at the moment to have a common EU-FDA document. The text remains unchanged.

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		unusual amount of equipment corrosion or wear is anticipated as a result of the manufacturing process, no further assessment is expected."	
146	1	Comment: It should be clarified that these requirements are only applicable to finished product packaging materials. Proposed change: Please change "Elemental impurities leached from primary packaging" to "Elemental impurities leached from primary packaging of the finished product"	Accepted. Primary packaging of the medicinal product is meant here. The text has been amended as proposed.
146 - 156	1	Comment: This section imposes higher requirements on liquid and semi-liquid dosage forms compared to the draft FDA GfI 255. FDA does accept compliance statements (to USP and CFR) from packaging manufacturers. In these cases, the MAH is not requested to repeat the extractable testing. In the absence of such a statement, testing of containers according to the heavy metal test is considered acceptable. In the spirit of international harmonization, it is proposed to adopt an approach more similar to the FDA approach. Proposed change: Please replace lines 154 to 156 by: "If the supplier certifies that the materials of construction of the primary packaging meet the applicable requirements of the European Pharmacopoeia and/or the food or cosmetics regulations, the MAH will not be asked to confirm the results for extractable metals. If a statement or data are unavailable from the	Partly accepted. The scope of the reflection paper is veterinary medicinal products authorised or to be authorised in the EU. There is no intention at the moment to have a common EU-FDA document. The text has been amended to reflect that extractable study should be conducted only if necessary.

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		manufacturer of the primary packaging regarding elemental impurities, EMA recommends performing at a minimum a test for heavy metals, such as the procedure previously described in Ph. Eur. 2.4.8, for containers used for liquid and semi-solid dosage forms."	
162	1	Comment: Text states that analytical data and risk assessment are required. If the risk assessment concludes that there are no potential sources of elemental impurities, analytical testing should not be required. Proposed change: Please modify the sentence to read: "However, if a risk assessment does not identify any potential sources of elemental impurities, analytical data are not required.	Not accepted. In the medicinal product approach, data concerning elemental impurity levels should be available and accompanied by a risk assessment. The text remains unchanged.
168	1	Comment: "… providing data from at least three representative production scale batches or six representative pilot scale batches of the medicinal product." The scale of the batch should not impact the level of elemental impurities. Proposed change: Please modify the sentence to read: "… providing data from three representative production scale batches or at least one production scale batch and two pilot scale batches of the medicinal product…"	Partly accepted. The number of batches for which results are shown should be commensurate with the risk. The text has been amended accordingly.
198	1	Comment: It is stated that any element known to be added, should be included in the risk assessment. Elements such as Cu and Se are present in products for treatment of deficiency and thus added	Partly accepted. The scope has been updated to exclude elements that are intentionally included in the medicinal product for therapeutic

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		intentionally. They should be controlled by a specification in the final product drug substance and not considered for the risk assessment. Proposed change: Please modify the sentence to: "Any element that is not intentionally added and controlled by final product specifications, should be included in the risk assessment."	benefit. No change is therefore considered required in section 5.
189 - 199	1	Comment: The list of elements to be considered matches the list in ICH Q3D; however, in the draft reflection paper it is not immediately apparent that the full list of elements in line 192 should only be assessed if intentionally added. According to ICH Q3D, a risk assessment is required only for class I and class 2A elements that are not intentionally added– not for the full list of elements. In addition, draft FDA GfI 255 requires the risk assessment for not intentionally added elements only if those belong to class 1. In the spirit of international harmonization, it is proposed to adopt the draft FDA approach. Proposed change: Please replace lines 191 – 196 by "At a minimum, a risk assessment should evaluate if arsenic, lead, mercury, cadmium, and any additional elements described in table 5.1 of ICH Q3D used in the excipient, drug substance, and drug product manufacturing process, such as catalysts, could be introduced into the finished drug product."	Not accepted. The scope of the reflection paper is veterinary medicinal products authorised or to be authorised in the EU. There is no intention at the moment to have a common EU-FDA document. The reflection paper states that the consideration of table 5.1 of the ICH Q3D are also applicable to veterinary products: if not intentionally added, inclusion of an elemental impurity in the risk assessment will depend on its class and the route of administration of the finished product. The text remains unchanged.
191, 193-196	1	Comment: Makes reference to ICH guideline Q3D to discuss toxicology and classes for different elemental	Not accepted.

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		impurities while it has been agreed that this guideline cannot easily be applied to veterinary medicines. Proposed change: Information specific to veterinary medicines should be included.	The RP states that the principles of the ICH Q3D are applicable to veterinary medicines, including the classification of elemental impurities without any further justification. The text remains unchanged.
201-204	1	Comment: "PDE values detailed in ICH Q3D are considered acceptable to ensure the quality of veterinary products but do not account for differences in species, metabolism, dietary requirements." The human PDE is calculated taking into account the arbitrary adult human body mass for either sex is 50kg. Proposed change: Section should be amended to include specifics for animals. See below: A scientific upgrade may be proposed for the animal medicinal products: Calculate the PDEs for any elemental impurity according to the standard body weight of target species from the official Eudralex database (Ref. 1). The same standard weights are used in the USA as there are no standards set specifically for USA. A similar proposal was already present in the current VICH guideline on residual solvents (Ref. 2): "*Option 3a: The applicant may provide an appropriate body weight for the actual target species and/or the actual dose and recalculate the PDE and/or concentration limit using the ICH equations and ICH supporting toxicological data."*	Accepted. The text has been amended to reflect the possibility to recalculate a PDE based on the weight of the target species.

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		Ref. 1: European Commission. Eudralex database.Vol.9B. *Guideline on Pharmacovigilance for medicinal products for veterinary use*. October 2011. §6.3.1.4 page 51/165. Ref. 2: VICH GL18(R): Impurities: Residual solvents in new veterinary medicinal products, active substances and excipients. EMA/CVMP/VICH/502/99-Rev.1§3.3. Sept.2011.	
200 - 214	1	Comment: Footnote 2 to the table in section 7 mentions that an elemental impurity will be considered absent if below 30% of PDE in 3 representative commercial batches or 6 representative pilot batches". However, this part of the control strategy should also be explained in section 6 to ensure the footnote is not considered to be just an example, but to be binding. In addition, the footnote is currently unnecessarily restrictive (see below). Proposed change: Insert in section 6 "If the total elemental impurity level from all sources in the drug product is observed or predicted to be consistently less than 30% of the PDE, then the element is considered absent. Where analytical results are presented, data on 3 representative commercial batches or 6 representative pilot batches or 1 representative commercial batch and 3 pilot scale batches are expected. When only lower numbers of batches are available (e.g. during marketing authorization application	Partly accepted. The corresponding footnote in section 7 has been included in the text and amended as relevant. If testing occurs, analytical data will have to be provided for new marketing authorisations. In case of variations/significant changes, no data should be provided post approval unless the control strategy in place has changed as a result of the outcome of the risk assessment. Documentation on calculation option should be provided as indicated in section 7.

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		or significant process changes), a commitment should be given to provide the data post-approval. Where a calculation following the component approach outlined in section 4.3.2 is provided, this should be documented."	
227 - 229	1	Comment: The expectation of having 3 representative commercial batches or 6 representative pilot batches is not realistic during marketing authorization applications for newly developed drug products: it is possible to file a marketing authorization application based on 3 pilot scale batches. Provision should be made for these cases. Proposed change: Please refer to section 6 and change to "an elemental impurity will be considered absent when the conditions outlined in section 6 are met"	Partly accepted. See comment above.
235-236	1	Comment: It is said that "the method to control any elemental impurities should be selective" and that "a non-specific compendial test for heavy metals will not be accepted". In some cases (e.g. inorganic excipients accounting for a small fraction of the drug product composition), a non-specific test would be sufficient to control risks. Proposed change: Please modify the sentence to read: "A non-specific compendial test for heavy metals will not be accepted unless it is specifically supported by the risk assessment analysis."	Not accepted. The heavy metals test Ph. Eur. 2.4.8 is not selective and is not considered appropriate to detect and quantify individual elemental impurity. The text remains unchanged.