EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Overview of comments received on "Guideline on the risk management requirements for elemental
(EMA/CVMP/426245/2023)

Name of organisation or individual	General or Specific comment	Line nr.	Comment and rationale	Proposed changes / recommendation	Outcome
Access VetMed	General	0	Access VetMed do appreciate the opportunity to comment on this proposed Guideline. Some minor suggestions/comments are enclosed in the following sections.		
Access VetMed	Specific	67	Access VetMed would support the initiative from AhE presented on IWP Interested Parties meeting (Oct24) and would suggest modifying the wording as follows.	This guideline applies to all categories of VMPs: VMPs other than biologicals, biological VMPs other than immunologicals and immunological VMPs unless otherwise justified.	**Not accepted.** The need to control the elemental impurities in VMP using the principles of risk management is mentioned in the Ph.Eur. Monograph 2619 on pharmaceutical preparations, and the Ph. Eur. Texts are legally binding for veterinary medicinal products.
Access VetMed	Specific	68	Access VetMed would support the initiative from AhE presented on IWP Interested Parties meeting (Oct24) and would suggest modifying the wording as follows.	This guideline also applies to novel therapy VMPs unless otherwise justified.	**Not accepted.** see comment above
Access VetMed	Specific	202	It should be noted that although ICH Q3D is out of scope for: (human) vaccines, DNA products, gene and cell therapy, tissue engineering, it is still applicable to Veterinary IVMP and biological VMP other than immunological. The information seems contradictory and should therefore be clarified to avoid any misunderstanding.		**Noted.** VMPs are soutside the scope of the ICH Q3D. The Eur.Ph. texts are legally binding for VMP, and the Eur.Ph. monogrpah for Pharmaceutical Preparations (2619) mentions that "manufacturers of (products outside the scope if the ICHQ3D) remain responsible for controlling the levels of elemental impurities using the principles of risk management". The aim of this guideline is to provide guidance on how such risk management can be conducted. The principles of the ICH Q3D are considered acceptable to fullfill this Ph.Eur. requirement. by providing some frame for an harmonised approach for all VMPs.
AnimalhealthEurope	General	0	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.		**Comment acknowledge.**

AnimalhealthEurope	General	0	1- Contradiction to EMA action plan (to improve the predictability of requirements and to reduce the financial burdens) As it was agreed and declared by European Medicines Agency (EMA), EMA and its partners in the European medicines regulatory network have implemented an action plan (EMA/239617/2016) to support the availability of veterinary vaccines in the EU. As a part of this action plan EMA committed to improve the predictability of requirements and to reduce the financial burdens of the veterinary pharmaceutical companies*. However, this new requirement seems to be not compliant with these aspirations as it was already explained in the comments on the related concept paper. * EMA/239617/2016: The type of impact on veterinary vaccine availability, including a reduction of financial or development time burdens, an increase in predictability of requirements or a positive impact on the 3Rs principle. As it was agreed and declared by European Medicines Agency (EMA), EMA and its partners in the European medicines regulatory network have implemented an action plan (EMA/239617/2016) to support the availability of veterinary vaccines in the EU. As a part of this action plan EMA committed to improve the predictability of requirements and to reduce the financial burdens of the veterinary pharmaceutical companies*. However, this new requirement seems to be not compliant with these aspirations as it was already explained in the comments on the related concept paper. * EMA/239617/2016: The type of impact on veterinary vaccine availability, including a reduction of financial or development time burdens, an increase in predictability of requirements or a positive impact on the 3Rs principle. Including vaccines and novel therapies in the scope of the guideline could create unnecessary regulatory burdens that do not contribute meaningfully to animal safety or product quality, especially since target animal safety studies performed during product development already supports that the potential presence of elemental impurities do not raise safety concerns.		**Noted.** The Ph.Eur. texts are legally binding for VMP, and the Ph. Eur. monograph for Pharmaceutical Preparations (2619) mentions that "manufacturers of (products outside the scope if the ICHQ3D) remain responsible for controlling the levels of elemental impurities using the principles of risk management". This guideline is drafted in order to provide guidance on how such risk management can be conducted. The principles of the ICH Q3D are considered acceptable to fullfill this Ph. Eur. requirement.
AnimalhealthEurope	General	0	2- Inconsistency with EP and ICH with regard to the application to VMPs The referred regulatory requirements laid down in Ph. Eur. 2619 on pharmaceutical preparations and ICH Q3D show also some inconsistency, especially in terms of IVMPs: Ph. Eur. 2619: Elemental impurities refers to General chapter 5.20. Elemental impurities which apply to pharmaceutical preparations except products for veterinary use, unlicensed preparations and other products that are excluded from the scope of this chapter. 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. ICH guideline Q3D as referred in Ph. Eur. 5.20: This guideline does not apply to herbal products, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellular blood components or blood derivatives including plasma and plasma derivatives, dialysate solutions not intended for systemic circulation, and elements that are intentionally included in the drug product for therapeutic benefit. This guideline does not apply to products based on genes (gene therapy), cells (cell therapy) and tissue (tissue engineering). In some regions, these products are known as advanced therapy medicinal products. Whilst VMPs are clearly excluded from the scope of Ph. Eur. 5.20 (ICH GL Q3D) in Ph. Eur. 2619, this new Guideline under public consultation makes these human requirements mandatory for VMPs without appropriate adjustment to the special needs of IVMPs.		**Comment acknowledge.** The aim of this guideline is to provide some information on how to conduct a risk assessment on elemental impurities to comply with the requirements of the Ph.Eur. monograph 2619 for elemental impurities. This guideline mentions specific considerations for IVMPs and for novel therapy products.

AnimalhealthEurope	General	0	3- Inconsistency with ICH with regard to application to vaccines and products based on genes Q3D(R2) guideline clearly states that vaccines and cell/gene therapy product are excluded from the scope of the ICHQ3D regulation in human: "This guideline does not apply to herbal products, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellular blood components or blood derivatives including plasma and plasma derivatives, dialysate solutions not intended for systemic circulation, and elements that are intentionally included in the drug product for therapeutic benefit. This guideline does not apply to products based on genes (gene therapy), cells (cell therapy) and tissue (tissue engineering). In some regions, these products are known as advanced therapy medicinal products." It is questionable on why it should be implemented for veterinary vaccines and novel therapy products as the main elemental impurities contributors would be the same for both the human and veterinary products: excipients, equipment, container closure systems. So, considering that those products are excluded for the Human area i.e. no safety issues expected, it should be the same		**Not accepted.** See comment above in line 19 : The requirement of risk assessment for EI is due to changes in the general monograph Eur.Ph. 2619 on Pharmaceutical prepartions and the principle of the ICH Q3D are considered acceptable to ensure the quality and the safety of VMPs. It is considered beneficial for an hamonised appraoch to provide guidance on how to perform such risk assement for all VMP and the principle of the ICH Q3D are considered acceptable for VMP.
AnimalhealthEurope	General	0	4- Inconsistency with the other VICH impurity GL In the VICH impurity guidelines (VICH GL10, 11, and 18), the term "vaccine" is not mentioned at all, but biological/biotechnological drug substances are explicitly excluded. This GL would therefore be inconsistent with the VICH impurity GLs.		**Not accepted.** The wording used in this EU guideline reflects the different types of products as mentioned in the Regulation (EU) 2019/6 that refers to the following products : VMP other than biologicals, biologicals products other than immunological products and biologicals immunologicals products, novel therapy products. As VICH guidelines apply accross different regions, the terms used to define the scope of each GL may be different between EU and VICH guidelines.

AnimalhealthEurope	General	0	5- EI represents negligible risks for immunologicals We would like to highlight again the significant concern regarding the addition of the biological immunological products to the scope of Elemental Impurities (EI), and its low relevance considering the composition of these products and their mode of administration, as commented on the Concept paper prior to this GL. It seems to have been partially taken into account by regulators since Specific considerations/particularities for IVMP are included in a dedicated chapter indicating that the risks are low for immunologicals. However, this addition still represents an additional workload and administrative burden for industrials which does not seem justified for this topic (benefit/risk ratio). As already indicated previously (at the time of consultation phase on the concept paper), the need to include immunological veterinary medicinal products (IVMPs i.e. mostly veterinary vaccines) in the scope is questioned considering their specificities discussed in the specific comments on text below. As a general note, it should be reminded that vaccines are excluded from the scope of ICH Q3D guideline which is referenced several times in this EMA/CVMP/426245/2023 (draft) and elemental impurities risk assessments are not required for vaccines for human beings. Additionally, it is recognized in this draft guidance that for IVMPs, the risks of elemental impurities being present at levels that raise target species safety or consumer safety concerns are considered generally low". Consolidation proposal: As acknowledged in the GL, considering 1- the production methods of immunological veterinary medicinal products (biological production processes do not typically introduce elemental impurities at levels found in chemically synthesized medicines), 2- the composition of vaccines (high number of starting materials and constituents at very low quantities), 3- the limited exposure due to their mode of administration (small volumes administered only on a few occasions – or just once – over the lifetime of animals and typically with long intervals between booster doses), it seems unrealistic, unjustified, and disproportionate to request that vaccines are assessed for elemental impurities as described in ICH Q3D. Especially since target animal safety studies performed during product development already supports that the potential presence of		**Partly accepted.** As already mentioned the requirement for a risk assessment on elemental impurities in VMP is a requirement from the general monograph Ph.Eur. 2619, and this guideline provide infrmation on how such risk assessment can be conducted. This requirement applies equally to all VMP. The principle of the ICH Q3D are considered acceptable to ensure the quality and safety of VMP. It is acknowlege that the risk for EI in IVMP is low and the considerations mentioned can be part of the risk assessment provided for the IVMP. The section 9 has also been reviewed to provide further considerations for these types of products.

AnimalhealthEurope	General	0	6- PDE and component approach are not appropriate for IVMPS It is not deemed reasonable to rely on human toxicological data at evaluation of the possible risk to different target species, while the veterinary pharmaceutical preparations are required to be developed with full consideration of the unique physiological and epidemiological needs of each target species. The guideline, now applicable to pharmaceutical and biological products, is based on the previous reflection paper on risk management for elemental impurities in veterinary medicinal products (EMA/CVMP/QWP/153641/2018), and therefore includes information/requirements that do not really apply to biologicals (for instance PDE approach). As commented on the Concept paper, an appropriate targeted approach applicable to IVMPs would have been welcomed (specific guideline for instance). The relevance of elemental impurities in VMPs is not well-justifiable either from legal or scientific point of view. In our opinion, the level of EI in VMPs has been adequately controlled based on the existing legal requirements laid down in European Pharmacopoeia and GMP guidelines. It should also be noted that the referred ICH guideline aims to make the human pharmaceutical companies apply a risk assessment-based approach to control elemental impurities in drug products (for human use) in the light of the Permitted Daily Exposure (PDE) values established by using human data. PDE established in ICHQ3D takes into account the possibility of accumulation of impurities following long term treatment with daily administration, which is not the case for vaccines. PDE levels should be revised for immunologicals (vaccines) taking into consideration this very limited exposure. Section 9 provides "Specific considerations/particularities for immunological veterinary medicinal products" which indicates (276-278) "for IVMPs... the risks of elemental impurities being present at levels that raise target species safety or consumer safety concerns are considered generally low". The reasons for this low risk are listed in 4 bullets on lines 280-288. Amongst these 4 bullets, the first (line 280) and the fourth (line 287-288) apply not only to the active substance but also to the IVMP finished product with the consequence that the sentence on lines 289-290 could be extended to the IVMP finished product. Using the		**Partlly accepted**. While the PDE in the ICH Q3D have been etablished for human products, these values are considered acceptable to ensure the safety of all veterinary medicines, including IVMPs. The specific reference to the component approach has been deleted and it is now mentioned that the component and the product approach are examples on how such risk assessment can be conducted. Other approaches may be used. For the PDE, the guideline gives the possibility to have level above the PDE if justified. The fact that the injected volume is low and that the administration is on annual basis is considered to be part of the risk assessment to demonstrate that the risk of EI is low in IVMP. It is acknowledge that the use of thiomersal in IVMP does not constitue a specific safety concern and his can be considered as part of the risk assessment.

AnimalhealthEurope	General	0	7- Lack of guidance on control strategy Reference is made to section 5 of the ICH Q3D which defines a control threshold as a level that is 30 % of the established PDE in the drug product. The control threshold may be used to determine if additional controls may be required. If the total elemental impurity level from all sources in the drug product is expected to be consistently less than 30 % of the PDE then additional controls are not required. If the risk assessment fails to demonstrate that an elemental impurity level is consistently less than the control threshold, controls should be established to ensure that the elemental impurity level does not exceed the PDE in the drug product. However, in this draft guidance, it is only mentioned that in case the level of a specific elemental impurity is proposed above the acceptable limit, additional measures should be considered to bring the levels below the acceptable limit. Please clarify if the "Guideline on risk management requirements for elemental impurities in veterinary medicinal products" only requires additional control measures in case the acceptable limit is exceeded The guideline states multiple times that a control strategy may need to be developed to assure that elemental impurities do not exceed the PDE's but does not outline the approaches that can be pursued as is done in ICH Q3D(R2). It is proposed to include a section on control of elemental impurities similar to section 6 in ICH Q3D(R2) to provide a clear guidance to the industry. The use of the terminology "acceptable limit" is confusing. In line 216-218 it is stated that "it is useful to convert the PDE to the concentration of the elemental impurity in the VMP to establish the acceptable limit that should be applied to the VMP". To our opinion permitted concentrations (µg/g) are not applicable for option 2b and therefore "acceptable limit" cannot be used as a general term. Please clarify if full validation of the test method is required for preliminary testing. We expect to be faced with an unexpected workload to carry out the requested risk assessment and to be, theoretically at least, faced with technical difficulties in implementing the required measures in the event of a negative conclusion of the risk assessment associated with significant investments, at least for marketed products. Indeed, how to manage that point for biological products (complex matrix to		**Partly Accepted.** It has been clarified that when the EI level is below or at the PDE no specific control for the EI(s) is needed. The text has also been further elaborated to give examples of approaches on how levels of EI can be reduced along the manufacturing process. The same wording as in the ICH Q3D is now used "permitted concentration limit". The methods used for EI impurities should be fit for purpose and specific. When a method is used for screening purpose, no full validation is expected, but the method should be specific for the EI to be analysed and sensitive enough to have accurate estimation. When a control is introduced for an EI for a source/material, the usual regulatory requirements applies for its description and its validation in the dossier.
AnimalhealthEurope	General	0	8- Reflection of the risk assessment in the registration dossier The risk assessment is a quality document under the responsibility of the manufacturing sites (falling under GMP). As such, a certificate stating the availability of the assessment and the risk conclusion is considered sufficient for the dossier.		**Not accepted**. Risk assessment for EI is a part of the control strategy for impurities for the VMP and not a GMP requirement. The summary of the risk assessment is required in the dossier for new medicinal product. Its maintainance can be handle under PQS, but it should be provided in support of a variation when the control stragtegy for an Elemental impurity needs change(s) in the dossier content.

AnimalhealthEurope	General	0	9- Conclusion In our opinion, requesting assessments according to ICH Q3D for VMPs should therefore be limited to products for which this is reasonably feasible which should exclude vaccines as foreseen by the scope of ICH Q3D itself. If however the Authorities decide to keep IVMPs in the scope of the guidance addressing EI, options to improve the workload-benefit balance of these requirements could further be evaluated: 1- evaluation restricted to only excipients, primary packaging, equipment and environment 2- exclusion of companion animals from the guideline as they do not represent a risk for food safety, 3- define a threshold (volume administered on a yearly basis or lifetime basis) below which assessment would not be required, 4- allow and define adjustment calculation for PDEs based on dose, target species, body weight, duration of treatment. An extended period to develop and put in place any testing would be essential. The industry will need clear guidance and advice regarding technical solutions. A step-by-step timetable for existing authorised products should be communicated.		**Partly Accepted.** It is aknowledge that the risk for Ei in IVMP is low due to the dose and the administration frequency. Further considerations in section 9 have been introduced.
AnimalhealthEurope	Specific	134-137	Comment: to align this section with the specific considerations/Particularities for immunological veterinary medicinal, it would be helpful to mention that since contribution of the active substance is considered as negligible for IVPMS, the risk assessment doesn't need to include evaluation of the active substance.	-	**Not accepted.** Actice substance is part of the finished product and can be a potential source of EI. Further specific considerations have been introduced in section 9 for IVMPs.
AnimalhealthEurope	Specific	175-179	Comment: …providing data from at least three representative production scale batches or six representative pilot scale batches of the VMP. When the risk is demonstrated to be low, data on at least one representative production scale batch and two representative pilot scale batches of the VMP may be provided… ICH training module 5 recognizes that manufacturing equipment is a lower risk source of elemental impurities since GMP policies, processes and procedures ensure that the contribution of elemental impurities from this source is low. The batch size of the tested batches is therefore not relevant as the contribution from the other potential sources is not dependant on the batch size.	Please modify to.. providing data from at least three representative batches (production scale or pilot scale or any potential combination (i.e. one production scale and two pilot scale batches)…	**Partly accepted.** It is acknowledge that when the risk is low, scale up would not be a concern for EI content. Data on 3 commercial or 6 pilot batches represent the expectation to estimate EI content. When such batch data are not available, a justification can be provided as part of the risk assessment. The wording has been slightly amended.
AnimalhealthEurope	Specific	206	Table 5.1 of ICH Q3D does not include the in-ovo route of administration. Clear guidance on how to deal with such a route of administration should be given.	Please modify to.. providing data from at least three representative batches (production scale or pilot scale or any potential combination (i.e. one production scale and two pilot scale batches)…	**Not accepted**. Information are already available on potential approach to recalculate the PDE when the administration route of the medicinal product is different than those mentioned in the ICH Q3D. No further information is considered needed in the GL. The approach taken should be explained in the risk assessment.
AnimalhealthEurope	Specific	206	Table 5.1 of ICH Q3D does not include the cutaneous route of administration. Please include Table A.5.1. as well.	-	**Accepted.** Reference to table A 5.1 has been added as this table lists the EI to consider in the risk assessment for the cutaneous and transcutaneous route.
AnimalhealthEurope	Specific	215	How to convert the human limit (per individual) to veterinary product limits knowing that animals vary significantly in bodyweight?	... be considered in the risk assessment given in tables 5.1 and A.5.1 of ICH Q3D are considered acceptable....	**Not accepted**. The ICH Q3D in section 7 provides information on how the conversion from PDE to maximum permitted concentration limit can be made, depending in the option calculation. Such reference is already present in the document and it is not considered needed to add further information here.

AnimalhealthEurope	Specific	218	It is useful to convert the PDE to the concentration of the elemental impurity in the VMP to establish the acceptable limit should be applied to the VMP. Options 1, 2 or 3 detailed in ICH Q3D (Section 7) may be used to establish the concentrations of elemental impurities in VMP or components that ensure that the VMP does not exceed the acceptable limits. This is very confusing as ICH Q3D (section 7) describes that the provided options can be used for converting PDE's to concentration limits and not acceptable limits which is a non-defined term.	Chapter 6 that accepts justification of levels of elemental impurities higher than the ICH Q3D PDE based on recalculation of the bodyweight of target species. If required, PDEs can be recalculated for animals with a bodyweight of more than 50 kg using the formula included in appendix 3 of the ICH Q3D for individual safety assessments.	**Accepted.** Reference to the calculation formula in appendix 1 of the ICH Q3D is mentioned in section 6 of the GL. Nevertheless, this approach is subject to the authority approval.
AnimalhealthEurope	Specific	227	"such higher levels are subject to authority approval". Vaccines fall by default under a reduced dose and duration of treatment and would therefore be allowed a higher level of elemental impurities. However, these can only be applied after authority approval meaning that theoretical calculations are limited to the lowest (human) PDE values despite the general acceptance that vaccines are by default in the low-risk category regarding elemental impurities.	It is useful to convert the PDE into concentrations of elemental impurities in VMP or components that would assure the daily intake of elemental products from the VMP does not exceed the PDE. Option 1, 2, or 3 detailed in ICH Q3D (section 7) may be used to calculate the permitted concentration. Also, adjustment calculation for PDEs based on dose, target species, body weight, duration of treatment is possible.	**Not accepted.** The GL already mentions the approach to recalculate the PDE for a specific target species in section 6. Dose and duration of treatment, target body weight as basis for possible adjustements/recalculations are already captured in that section. Any level higher than the PDE of ICH Q3D is subject to authority approval. No change is considered needed here.
AnimalhealthEurope	Specific	232	Difference must be made between the documentation to be maintained in Company Pharmaceutical Quality System (full quality risk assessment) and the documentation to be included in regulatory dossiers (summary report). See training materials of the ICH Q3D, module 5 on risk assessment. The level of details requested for this summary report seem to be exaggerated.	Please change this to "such higher levels should be scientifically justified"	**Not accepted.** The elements/documents/information to be provided in the dossier should be sufficient for the assessors to understand how the risk assesment was perfored and any limit calculated when relevant. The elements mentioned are considerd the minimum to be provided to fully assess the risk of EI for that product. Nevertheless, some flexibilities are considered possible for IVMP.
AnimalhealthEurope	Specific	250-251	As IVMPs have just been added to the scope of IE guideline, part 2E of the dossier of the already registered products de facto does not include summary reports of the risk management for IE and will only be updated accordingly when relevant (i.e. when the outcome of RA demonstrates that a variation to update the dossier is necessary). The sentence as written should be modified.	Therefore, it is proposed to reduce the elements present in the summary report down to a relevant subset of the elements from the full quality risk assessment dossier. It should be demonstrated that a complete Risk assessment on the presence/absence of elemental impurities has been performed. The strategy of control used, and, in line with ICH Q3D chapter 5 § 5.6, a justification of impurity level and control threshold should also be presented.	**Not accepted.** For products already on the market, there is no need to include in the dossier the conclusion of risk assessment when it has been demonstrated that the level of EI is below the relevant PDE. There is no need to declare that such risk assessment has been conducted. The conclusion of the risk assessment should be available on site. If as a consequence of the Risk assessment for a marketed product, there is a need to include a control for an EI, the data to be provided in the dossier should be sufficient for the Competent Authorities to understand how the risk assesment was perfored and any limit calculated if relevant. The elements mentioned are considerd the minimum to be provided to fully assess the risk of EI for that product. Some flexibilities are considered possible for IVMP.
AnimalhealthEurope	Specific	268-270	A phased-in implementation of the risk assessment for elemental impurities in biological veterinary medicinal products shall be proposed, precising targeted dates to conduct risk assessments, and considering either new biological veterinary products or registered products authorised before the date of implementation of Elemental impurities Risk Assessment.	"The summary report of the risk management should always be provided in part 2E of the dossier when relevant to justify the presence/absence of control strategy for elemental impurities."	**Accepted.** A phase implementation is proposed for IVMP. This is detailed in Implementation of submission of risk assessments to control elemental impurities required by the European Pharmacopeia in immunological veterinary medicinal products EMA/CVMP/366323/2025**.**

AnimalhealthEurope	Specific	274-307	for the reasons mentioned above, AnimalhealthEurope continues to recommend that IVMPs are completely excluded from the scope of the guideline. If this is not possible, this exclusion of IVMPs from the scope of this guideline could be conditional (it could be based on a dose volume threshold for example e.g. "IVMPs are not in the scope of this guideline as long as, per their label, not more than 100 ml is administered to an individual animal on a yearly basis"). And if this is still not possible, we would at least strongly suggest evaluating the following options: 1- evaluation restricted to only excipients, primary packaging, equipment and environment 2- exclusion of companion animals from the guideline as they do not represent a risk for food safety, 3- define a threshold (volume administered on a yearly basis of lifetime basis) below which assessment would not be required, 4- allow and define adjustment calculation for PDEs based on dose, target species, body weight, treatment duration.		**Partly accepted.** As the requirement arises from the Eur.Ph that is legally binding, all VMPs are concerned by such requirement and there is no exclusion possible. It is acknowledge that the risk is low for IVMP and the section 9 specific to IVMP has been reviewed to further reflect it.
AnimalhealthEurope	Specific	274-307	"An appropriate approach to establish the risk assessment for IVMP's could be done similarly to the component approach as described in section 4.3.2". However, section 4.3.2 states all potential sources of elemental impurities should be taken into account e.g. active substance, excipients primary packaging equipment and environment. It is already clearly described in lines 279-290 that the contribution from active substance is negligible. This, in addition to the fact that it would be extremely complex to address the EI for active substances (antigens) used in vaccines (as explained above) and require extensive resources to address a theoretical risk, leads us to propose to completely remove active substances (antigens) from the scope of this guideline (if it is not possible to exclude IVMPs entirely off the scope). Further, it should be clarified that organomercuric compounds such as thiomersal should not be taken into account as the ICH Q3D states that the PDE established does not apply to organic mercury. Safety assessment for such compounds should performed outside of the guideline.		**Partly accepted**. Section 9 has been amended further to reflect that the risk for EI for IVMP is low. The considerations of the ICH Q3D on the organic mercury can be part of the risk assessment when such compounds are used in a medicnal product.

AnimalhealthEurope	Specific	276	Production process is part of the risk assessment itself. The fact that a manufacturer uses a well-known process is one of the justifications in the risk assessment and should be extended to novel therapy products also.	Please change the text to read: "An appropriate approach to establish the risk assessment for IVMP's can be done taken in account following potential sources only: excipients, primary packaging, equipment and environment. For excipients, it should be noted that all organomercuric preservative compounds are not in scope of this guidance. "(…) As such, theoretical risk assessment and specific controls on elemental impurities up to the active substance level are generally not needed unless otherwise justified". "(…) Risk factors that should be considered in this assessment should include: • the type of excipients used, • the manufacturing process conditions, • their susceptibility to contamination by environmental sources (e.g. controlled areas for sterile manufacturing and use of purified water) and • overall dosing frequency. An appropriate approach to establish the risk assessment for IVMPs could be done similarly to the component approach as described above in section 4.3.2. "The component approach", but considering only excipients, primary packaging, equipment and environment. Organomercuric compounds such as thiomersal should not be taken into account (as the ICH Q3D states that the PDE established does not	**Partly accepted.** Section 9 has been amended further to provide additional considerations for IVMP. Such considerations on the manufacturing process can be included in the risk assessment for a medicinal product.
AnimalhealthEurope	Specific	289-290	The following sentence addresses the level of biological active substance for which it is agreed that specific controls are not required, unless otherwise justified. The term "generally" is redundant in the following sentence.	"For IVMPs manufacturer in well-known production processes, the risks of EI being present,..... are considered generally low"	**Accepted**. The term "generally" has been deleted as proposed.
AnimalhealthEurope	Specific	296-297	"Risk factors that should be considered in this assessment should include: -the type of excipients used".	"As such, specific controls on EI up to the active substance level are generally not needed unless otherwise justified".	**Partly accepted.** Section 9 has been amended further to provide additional considerations for IVMP.

AnimalhealthEurope	Specific	274-307	In addition to the specific aspects already outlined in the draft guideline for IVMPs, the following aspects should be taken into account in a general risk assessment of potential EIs in these products: IVMPs are pharmaceutical preparations which: - contain live or inactivated micro-organisms (bacteria, viruses or fungi), parasites, antigenic fractions or substances produced by these organisms (e.g. toxins) or nucleic acids that are sensitive to physio-chemical effects; therefore, special conditions are required during their manufacturing process and the storage of final formula, excluding extreme conditions of acidity or alkalinity or heat. This unique feature reduces considerably the potential to leach or extract EIs from the immediate packaging materials and equipment used in their manufacturing process. - have limited shelf-life (max. 3 years) stored at maximum 2-8°C that also not favourable for chemical interactions with immediate packaging materials; - excipients can't be considered materials of special risk because these are mainly of Pharmacopeial quality, if not well-based justification is needed; - not used for long-term treatment but are administered only in small amounts and a few times in the lifetime of an animal and administration is repeated infrequently; - not exposed to environmental contamination during their whole manufacturing processes - not only in the active substance production but also at blending of the finished product - because IVMPs are produced with qualified equipment and in aseptic or microbiologically well-controlled conditions to ensure its stability throughout their shelf life as per Ph. Eur.0062 (3-8). - may contain only materials (e.g. adjuvants, preservatives) that contribute to its function and/or its use and all components are selected with care therefore it is not possible to replace with alternatives in most of the cases. The considerations already listed in the draft guideline, and supplemented by the assessment above, should lead to the conclusion that IVMPs are generally falling out of the scope of the guideline. This conclusion is	Please add adjuvants to read: "the type of excipients and adjuvants"	**Not accepted.** Adjuvents are covered by the word "excipients."
AnimalhealthEurope	Specific	304	Besides the use of real data, reference to articles "a compilation of metals and trace elements" and "materials in manufacturing and packaging systems and updated literature review" from D. Jenke et all. as referenced in the trace studies of the ICH Q3D training modules can be used to justify negligible risk of packaging material	Please change to read: "Data from leachable/extractable studies may also be used. If this data is not available reference to articles "a compilation of metals and trace elements" and "materials in manufacturing and packaging systems and updated literature review" from D. Jenke et all may be used in the risk assessment."	**Partly accepted**. It has been added the possibility to refer to bibiographic data as possible supportive data for the risk assessment.