18 November 2021
EMA/367323/2021
Veterinary Medicines Division

Overview of comments received on 'Guideline on veterinary good pharmacovigilance practices (VGVP)' (EMA/635856/2020)

Module: Collection and recording of suspected adverse events for veterinary medicinal products

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	Federation of Veterinarians of Europe (FVE)
3	German Environment Agency (UBA)
4	European Group for Generic Veterinary Products (EGGVP)

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	AnimalHealthEurope would like to thank the Agency for this important document and is grateful for the opportunity to comment. Please find some comments, some of them are minor/quite detailed but some others are major as they could have big impact on industrial operations. Should you have further questions, AnimalHealthEurope is happy to provide any clarification needed.	
2	FVE welcomes the EMA proposal on general guidance on the requirements, roles, activities and procedures related to collection and recording of suspected adverse events (AE) for veterinary medicinal products occurring within the EU/EEA or in third countries. We also welcome that the guideline requires the reporting of adverse events observed after off-label use of any medicinal product in animals or after accidental use, as it happens in cases of inadvertent doping. In order this guideline to become completer we suggest that 'inadvertent doping', which is often observed in horses, i.e. when an untreated horse is exposed to a veterinary medicinal product via a treated animal and is later on tested positive during an anti-doping test despite having never received any VMP directly. Such cases have been reported in the literature e.g. for NSAIDs which can be taken up by horses via straw/bedding that has been contaminated with urine from a recently treated horse. If events like this occur for a product, it would be good if a warning would be included into the SPC. We note that the scope of this module provides details on the principles and procedures for best practice on collection, reporting	

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	and recording of suspected adverse events for veterinary medicinal products for marketing authorisation holders, national competent authorities, the Agency and the Commission for safeguarding animal and public health and the environment. Nevertheless, FVE would like to highlight the need for developing also a guideline describing the principles for best practice pharmacovigilance intended in particular for veterinarians. FVE calls on EMA to consider the development of such a guideline and would very much like to collaborate with EMA about this.	
3	The existing pharmacovigilance system is de facto not able to ensure the environmental safety of medicinal products in use. Residues of medicinal products, especially active substances, are regularly detected in various environmental compartments. In some cases, such as highly potent substances like parasiticides or when active substances enter the environment in higher concentrations, adverse effects on the environment can also occur. However, these adverse effects are hardly ever recorded because the causal relationship with the use of a veterinary medicinal product often cannot be established and environmental effects are usually not actively monitored. This problem could be reduced if the pharmacovigilance system would also record the occurrence of active pharmaceutical substances in the environment. These measured environmental concentrations could then be compared with so-called PNEC values for environmental organisms (predicted no effect concentration), which are submitted, for example, as part of the authorisation procedure. In this way it could be assessed whether there is an adverse effect arising from the occurrence of an active substance in the environment or not.	

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	In our opinion, this is how the statements in recital 56 of regulation 2019/6 on environmental pharmacovigilance could be implemented in the pharmacovigilance system. Furthermore, the proposed procedure would be fully in line with the definition of "environmental incident" provided in the glossary.	
4	EGGVP is grateful for this draft guideline and also for the opportunity to comment. We also thank the EMA for the previous discussions on this topic, as it allows us to support in building an efficient new veterinary pharmacovigilance era in Europe. For this specific module on the collection and recording of suspected adverse events for veterinary medicinal products, we are happy to see that most points of concern or requests of clarification addressed in the past months have been taken on board – thank you for that.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
88-98	1	Comment: It should be clarified that the listed suspected adverse events should be linked to the MAH responsible for the VMP in question. Proposed change: Please add to sentence 87: **"...for which the MAH is responsible for."**	Not accepted. The guideline must be read in conjunction with Article 76(2) of Regulation (EU) 2019/6.
110-111	2	Comment: Proposed change (if any): …in an animal or a number of animals, **a flock or a heard** or…	Not accepted. A number of animals is a more general expression and it may include a flock or a heard.
114	1	Comment: There seems to be a duplication of the wording 'in line with' Proposed change (if any): "…. later than within 30 days from their date of receipt in line with the time frame stated ~~**in line with"**~~	Accepted. The guideline was corrected accordingly.
118m 234	2	Comment: Proposed change (if any): … **Peer-reviewed s**cientific literature is …	Not accepted. Specific reference to peer-reviewed and non-peer-reviewed literature is included in section 2.1.1.2.
121-123	3	Comment: In line with recital 56 of regulation 2019/6 also data on environmental incidents related to the active substance should be collected and assessed in the pharmacovigilance system. This could for example	Not accepted. The term "relevant databases" would cover all databases including those related to more specific information.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		include information on the concentration in environmental compartments or new information on ecotoxicological effects. Any new information could then be compared to the data used in the environmental risk assessment to detect any potential adverse environmental impact related to the use of the product which have not been known at the time of authorisation. Proposed change (if any): Please add *"and databases for environmental information related to the active substance"* as follows: Marketing authorisation holders are therefore expected to review scientific literature in line with their internal procedures using relevant databases for information related to their authorised veterinary medicinal products ***and databases for environmental information related to the active substance.***	
124-129	3	Comment: Environmental incidents should be explicitly mentioned. Proposed change (if any): Please add *"and environmental incidents"* as follows: Marketing authorisation holders should conduct such a review at least once a year, where necessary more frequently based on a risk-based approach, and	Not accepted. Environmental incidents are covered by the term "adverse events" (see Article 73(2) of Regulation (EU) 2019/6).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		ensure that any identified suspected adverse event reports ***and environmental incidents*** are recorded in the Union pharmacovigilance database…	
125	3	Comment: Guidance should be provided on how to apply the risk-based approach to environmental incidents. For instance, measured environmental concentrations of e.g. active substances (MEC data) could easily be compared with predicted no effect concentrations (PNEC values) in order to assess whether there is an environmental incident arising from the occurrence of an active substance in the environment or not. PNEC values are provided by the marketing authorization holders within the authorisation procedure. Proposed change (if any):	Partially accepted. It was agreed that no additional risk-based requirements for targeted signal management activities (including literature search) on environmental incidents would be established for all authorised products, however where necessary and for particular products, such review should be envisaged further to advice from e.g. the Environmental Risk Assessment Working Party (ERAWP).
135-142	1	Comment: The current wording is not clear what comes to review of local scientific journals, which are not indexed in global databases. To avoid interpretations resulting in different views between stakeholders it should be clarified what exactly is required in regard to those journals. E.g. currently some EU pharmacovigilance inspectors expect that MAHs should have procedures in place to monitor scientific and medical publications in local journals in countries where medicinal products have a marketing authorization. This interpretation has been adopted from guidelines concerning medicinal products for human use (Human GVP Mod VI chapter VI.B.1.1.2).	Not accepted. Local scientific journals may provide important safety information in the local language which cannot necessarily be captured in global databases.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		In new VGVP it should be clear that review of medical and scientific literature using relevant databases is what is expected for veterinary products. No additional systematic review of local scientific and medical publications is expected.	
136	4	Comment: It would be welcome if the guideline could make a clear statement here that the requirement for MAHs is for searches on brand name (MAH own product), not on active substance, in line with statements in lines 123 and 158.	Not accepted. Literature search should be sufficiently wide to capture all relevant articles, however MAHs are expected to only collect information related to their authorised veterinary medicinal products in line with their internal procedures.
139	2	Comment: Proposed change (if any): … non-peer-reviewed local journals, **for example, a book or book chapter, a newspaper or magazine article, a website or blog post, a documentary film, or a document published by a government agency**, these…	Not accepted. The term "non-peer-reviewed local journals" is a general term and it is self-explanatory. In addition, websites, blog post, documentary film are covered by non-medical sources, internet or digital media (see VGVP module section 2.1.1.3).
154-156	4	Comment: Clarification is very much welcome	Accepted. The guideline was amended accordingly and the sentence in lines 154-156 will be deleted. Lines 162-170 cover the reporting requirements for adverse events from any non-company sponsored digital media or non-medical source of which the MAH becomes aware.
164	1	Comment: 'company sponsored digital medium' should read 'company sponsored digital media' as elsewhere in the document for consistency.	Accepted. The guideline was amended accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please modify the sentence to read: **"...company sponsored digital media..."**	
165 f.	3	Comment: We recommend to provide some guidance which kind of environmental information should be reported. Proposed change (if any): Please add the following sentence after line 165 ("…prior to the 'Due date' set for the signal management procedure for each of their authorised veterinary medicinal products." ***'Regarding environmental incidents, the literature review should include literature on potential adverse effects, but also literature on hitherto unknown adverse effects observed in laboratory studies and field studies as well as monitoring data on occurrence in the environment. These data should be reported for both, the active substance and the medicinal product, as applicable.'***	Not accepted. This proposal was not considered acceptable as it goes beyond the requirements for adverse event reporting, it would cause administrative burden and a potential duplication of information of similar products and generics. It was agreed that no additional risk-based requirements for targeted signal management activities (including literature search) on environmental incidents would be established for all authorised products, however where necessary and for particular products, such review should be envisaged further to advice from e.g. the ERAWP.
172-173 & 223-233	1	Comment: Clarification is requested as to whether it should be considered as sufficient to be able to contact the reporting source e.g. via a contactable email address or whether the reporter needs to reply in order for the case to be considered a valid PV case. Confirmation is requested that an e-mail address is only considered an identifiable source if a response is received. Confirmation is also requested as to whether it would be sufficient to receive further	Not accepted. This is considered in line with similar guidance for medicinal products for human use.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		information via email without the adverse event reporting form being filled out by the reporter. Proposed change: Please clarify in the text that an e-mail address is only considered an identifiable source if a response is received.	
178	2	Comment: Proposed change (if any): … or new **drug** combinations) …	Not accepted. The text "new combinations" is self-explanatory.
181-183	4	Comment: It is a positive development that it is clarified that blinded studies do not have to be "de-blinded" in the running study anymore.	Accepted.
216-218	1	Comment: This seems to suggest there will be a requirement to record the contact details for the primary reporter at the local site of the notified organisation. This is a significant change to some MAH processes and may increase the administrative burden. The reference to local site should be removed. Proposed change: "Whenever possible, the contact details for the primary reporter should be recorded **~~at the local site of~~ by** the notified organisation (i.e. marketing authorisation holder or national competent authority) to facilitate follow-up activities."	Accepted. The guideline was amended accordingly.
244-245	2	Comment: Please clarify if you mean the adult animals or foetuses/young animals Proposed change (if any):	Clarification: "Animals" include both adult animals and foetuses/young animals.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
252-255	1	Comment: "environment incident(s)" in a narrowed sense of this definition, we do not have always an animal and therefore Environmental as described here is not always an AE (VICH) "Any observation in animals, …in humans …". However, this was already vague for the definition in Vol 9B. – If animals are involved where is the line, does this means the non-treated species described in the scenarios of section 2.18 (untreated animals exposure)? – VeDDRA: What is the difference between 'Environmental AE' and 'Accidental exposure' (2.18)? In the glossary, there is the term 'Environmental incident' now, before it was 'potential environmental problems' (Vol 9B) – Is this a change or should it be the same? – How to use VeDDRA code 'Environmental adverse event' without patients, as it is not an adverse event? Please clarify.	Partially accepted. The definition for environmental incidents includes situations where the treated animals are not directly affected. A proposal to amend the current VeDDRA term "Environmental adverse event" to "Environmental incident" is under discussion.
252-254	3	Comment: Currently there is only one VeDDRA term foreseen for environmental incidents ("other"). It is suggested to consider additional VeDDRA terms to better specify environmental information to be collected. Proposed change (if any): Environmental impacts should be more specified (e.g. impacts on which species, monitoring data on occurrence in the environment, etc.) and the VeDDRA terminology should be expanded accordingly.	Partially accepted. A proposal to amend the current VeDDRA term "Environmental adverse event" to "Environmental incident" is under discussion. The guideline was amended with the addition of the text as follows: "Any specific information regarding environmental incidents should be recorded in the case narrative".

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
263-264	1	Comment: This was already commented in previous drafts: if no product name and only active substance should the case be registered? Clarification is sought on what is exactly meant: The active substance name of an unknown product used concomitantly (beside the product of the MAH that reports the AE, of which the product name is known)? Or also cases without any known product, but with active substance that is present in one of the products of the MAH's product portfolio? In the latter situation, there is no product identified, so no four minimal points available. Please confirm that the phrase indicates the first option, and not the second one. Proposed change: Please delete the sentence "**Exceptionally…shall be recorded**" or alternatively clarify in the text that this is only applicable in the first situation described above.	Not accepted. This requirement applies both to the cases where there is the active substance name of an unknown product used concomitantly (beside the product of the MAH that reports the adverse event (AE), of which the product name is known) and also in cases where there is a known active substance as the only product information in the AE report. The Union pharmacovigilance database accepts this type of reports according to the system's business rules.
268-270	1	Comment: new in this section: "The number of animals affected by each AE should be recorded against the relevant VeDDRA Term" ⇒ MAH database may not allow this operation.	Not accepted. The marketing authorisation holders should endeavour to implement the VICH standards which allow the number of animals affected by each adverse event to be recorded against the relevant VeDDRA term.
277-283	1	Comment: This has become a very lengthy and wordy sentence, which does not make it easy to read. Proposed change: Please consider rewording.	Accepted. The text in the guideline was amended as follows: "The case narrative is very important and should contain all known relevant clinical and related information as provided by the primary reporter (i.e. original verbatim text reported by the primary reporter). This information

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			should also be recorded using the VeDDRA terminology, including animal or human or environment details, exposure or treatment details. The course of suspected adverse event(s) and a description of the suspected adverse event(s) including the outcome, diagnosis, and any other information regarding the suspected and concomitant medicinal products (e.g. laboratory test results, necropsy findings) should also be recorded."
278-279	1	Comment: Regarding the requirement '*…as provided by the primary reporter (i.e. original verbatim text reported by the primary reporter)…'*. How does this relate to the fact that the narrative is supposed to be presented in a logical sequence (see line 286 below)? The information as provided by the primary reporter may not allow for a comprehensive overview.	Not accepted. The original verbatim text reported by the primary reporter (e.g. the exact words used by the primary reporter) can be presented in a logical order in the case narrative.
285	2	Comment: Proposed change (if any): … parameters**, (i.e., body weight gain (FCR) and body growth)** …	Accepted. The guideline was amended as follows: "… parameters (e.g. body weight (Feed Conversion Ratio (FCR), body growth) …".
301	2	Comment: Proposed change (if any): …with **clinical** sequelae**.**	Accepted. The guideline was amended accordingly.
309	2	Comment: Make reference to 'inadvertent doping' as part of the accidental exposure to a medicinal product that needs to be reported.	Not accepted. The term "accidental exposure" already covers these cases, whenever adverse events are identified. Additional explanation may be added in the case narrative.

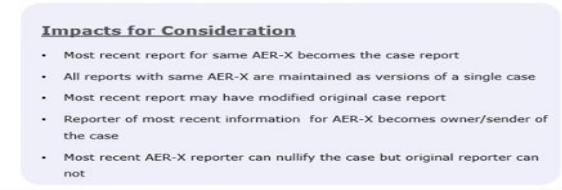
Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): …details on how the exposure occurred (e.g. accidental, **inadvertent doping'**), …	
319-321	1	Comment: MAHs are primarily responsible for signal detection and management, for which it is important to be able to have visibility to all relevant case information, as indicated by the last part of the sentence in line 321. However, this sentence does not include MAHs as being able to request translations. Proposed change: "Member States may record case narratives in their official language(s) and for those reports, case translations in English should be provided where requested by the Agency or other Member States, **or Marketing Authorisation Holder** for the evaluation of potential signals."	Not accepted. The text is in agreement with the relevant GVP module for medicinal products for human use.
325	1	Comment: Suspected and Concomitant medicinal product. There is no VICH definition for concomitant product, nor is this used by regulatory agencies / MAHs / different geographies in a consistent manner. It makes more sense and is more in the spirit of no causality assessment for all products to be considered suspect. Proposed change: Please delete section as this is not compliant with existing VICH guidelines.	Partially accepted. The guideline was amended as follows: "**Suspected medicinal product(s)/active substance(s) identification** All medicinal product(s)/active substance(s) included in a suspected adverse event report recorded in the Union pharmacovigilance database will be considered suspected during the process of signal management. It is recommended to record in the case narrative the opinion of the primary reporter identifying which medicinal product(s)/active substance(s) is(are) considered suspected, when available.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			If the attending veterinarian's assessment is available, indicating which products are considered suspected, this information should be also recorded in the case narrative. This information is of particular value when performing in-depth analysis for signal detection. The available field in the VICH (Veterinary International Conference on Harmonization) guideline on pharmacovigilance VICH GL42: "B.5.1. Attending veterinarian's assessment" can only capture this type of information at report level, without indicating the actual products, and therefore this field can be left blank. Furthermore, experience has shown that establishing and recording the potential causal association at individual case report level between all observed suspected adverse events and each of the concerned medicinal products by using a coding system, is often inaccurate, prone to bias, variable over time, and that it can cause a considerable administrative burden. With the institution of the signal management process (see VGVP module on Signal management) as the main pharmacovigilance tool, it is no longer considered necessary for the marketing authorisation holders or the national competent authorities to indicate their interpretation on the potential causal association for each of the medicinal products in the suspected adverse event report at individual case report level. The available fields foreseen by the international standards to collect this information (see VICH GL42:

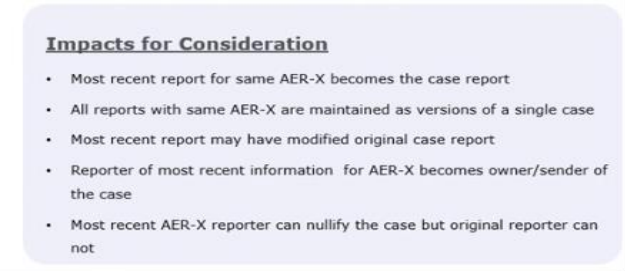
Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			"B.2.1.5. MAH assessment", "B.2.1.6. RA assessment"), can therefore be left blank."
372	2	Comment: Proposed change (if any): … dosage administered **(in mg/kg of bodyweight)** to individual target animals. In addition, information on **the class of** feed additives…	Not accepted. The dosage can be provided in various units (e.g. ml/kg etc). Class categorisation of feed additives is not relevant for pharmacovigilance.
377	1	Comment: As stated, this cannot be a requirement for a MAH, as the test may be carried out, but the reporter may refuse to provide the results to the MAH. Proposed change: "Necropsy findings should be provided if **information or outcome of** such tests were **provided ~~carried out~~.**"	Accepted. The guideline was amended accordingly.
395-396	1	Comment: As it is in general not seen necessary to add a comment on causality for adverse events reported in animals, it should not be mandatory to add the conclusion/comments to each suspected adverse event in humans. Proposed change: Please modify the sentence to read: "The conclusion/comments of the marketing authorization holder or national competent authority on the suspected adverse event(s) in humans provided in the case narrative **as applicable**."	Accepted. The guideline was amended accordingly.
395-396	4	Comment: In case of AEs in humans with veterinary medicines, it does not seem appropriate that the MAH	Partially accepted. The guideline was amended as follows:

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		adds conclusions to the case narrative. It may also not be possible for the national competent authority, as very often assessors of PV reports in veterinary pharmacovigilance are not physicians, but pharmacists or veterinarians. It is therefore not appropriate that assessments for human AEs are provided by assessors. The case narrative is also not considered the most appropriate place for adding the conclusions. Proposal: "*The conclusion/comments of the ~~marketing authorisation holder or~~ national competent authority, **as appropriate**, on the suspected adverse event(s) in humans ~~provided in the case narrative~~"*	"The conclusion/comments of the marketing authorization holder or national competent authority on the suspected adverse event(s) in humans provided in the case narrative as applicable."
420 ff	1	Comment: Should be read as "Any infectious organism, virus, or infectious particle, pathogenic or non-pathogenic, is considered an infectious agent. Excluded are the infectious active ingredients of a product (e.g., vaccination) administered to the patient." As an agent can be complete but not infectious, and an active ingredient in the vaccinated/treated animal is not an AE. Overall, this section is not clear and the examples are misleading. E.g: 1) Contamination of a product with an infectious agent (Bio and pharma), detection in patient: administration e.g. injection, source contamination(?)	Partially accepted. Subject to future discussions.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		2) Insufficient inactivation/attenuation of a bio product, detection in patient: administration e.g. injection, source contamination (?) 3) infectious active ingredients of bio product, detection in patient – NO AE (but what's if it is found longer than expected?) 4) infectious active ingredients of bio product, detection in non-treated patient – administration e.g. environment or air, licking, source contamination(?) 5) infectious active ingredients of bio product, detection in water – Environmental incidents? It would be appreciated more clarification on this section e.g. in future discussions of the guidelines.	
422-424	1	Comment: "*Transmission of an infectious agent may be suspected … or laboratory findings indicating an infection*…" This can be a wide field for all MLV products (and other bio /pharma products) with the new tools that are available.	Partially accepted. The text was amended as follows (addition in bold): "**Unintended** transmission of an infectious agent may be suspected from clinical signs in animals, clinical signs and symptoms in humans, or laboratory findings indicating an infection in animal(s) or human(s) or organism(s) exposed to a veterinary medicinal product."
443-444	1	Comment: 'Safety issue'? There is no clear distinction from environmental incidents and affection of non-treated animals. Which VeDDRA codes are meant here? Please clarify.	Partially accepted. The type of information should be "Safety issue" for the cases of transmission of infectious agent and 'Other' for the cases of environmental incidents. The VeDDRA term "suspected infectious agent transmission" should be used for the cases of transmission of infectious agent.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
452-453	4	Comment: In order to meet this section, it should be ensured that two VeDDRA terms are available, one for "suspected" and one for "confirmed" quality defects.	Accepted. This point is already under discussion.
465-467	1	Comment: According to the current text, only the original sending organization can nullify a report when identified as duplicate. However, the current nullification process proposed by EVVET 3 Best practice guide (see last two bullet points below) indicates that the sender of the latest case follow-up become the case owner and it is this organization that can nullify the report and not the case originator  	Partially accepted. The text: "When a duplicate has been identified that was recorded in the Union Pharmacovigilance database by the same original sending organisation, only this sending organisation can nullify one of the reports while ensuring that the remaining report contains all information present in the nullified report" was deleted in the guideline. In addition, the text: "After identification and confirmation, these reports will be merged into a single new (or merged) suspected adverse event report, known as the "master report" (see EU VICH adverse event report implementation guide)" was deleted in the guideline. Furthermore, the text: "The use of standard terminology for coding suspected adverse events by the marketing authorisation holders and the national competent authorities is essential, as the duplicate detection algorithm in the Union pharmacovigilance database relies on fields containing standard terminology to identify possible duplicates. The use of standard terminology serves to minimise the risk of duplicate suspected adverse event reports and the administrative burden associated with their subsequent management" was amended as follows:

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: harmonization between EVVET 3 business rules and this GPV should be made in terms of nullification process.	"The use of standard terminology for coding suspected adverse events by the marketing authorisation holders and the national competent authorities is essential, as the duplicate detection algorithm in the Union pharmacovigilance database will rely on fields containing standard terminology to identify possible duplicates. Thus, any organisation recording a suspected adverse event report in the Union pharmacovigilance database should ensure that it contains as much information as possible in order to facilitate the detection and confirmation of duplicates. The use of standard terminology serves to minimise the risk of duplicate suspected adverse event reports and the administrative burden associated with their subsequent management."
468-470	1	Comment: The EVVET 3 will not have this functionality developed by 28 January 2022 and there will not be no possibility to create a 'master report'. This functionality will only be developed later during 2022. Once this functionality is available in EVVet3 it should be possible for the MAH(s) of suspected products of the concerned cases to easily identify merged cases in EVVet3. Ideally, the MAH(s) should be made aware of the new merged case including the information which case was identified as a duplicate and merged into the new case. This is important for the MAH(s) to conduct signal detection. The current proposed functionality, contrary to the 'master report' concept will result in any new follow-up information to the initial case report to become	Accepted. The text: "After identification and confirmation, these reports will be merged into a single new (or merged) suspected adverse event report, known as the "master report" (see EU VICH adverse event report implementation guide)" was deleted in the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the case report (i.e. most recent information may have modified the initial case report – see the first three bullet points of EVVET3 business rules).  **Impacts for Consideration** • Most recent report for same AER-X becomes the case report • All reports with same AER-X are maintained as versions of a single case • Most recent report may have modified original case report • Reporter of most recent information for AER-X becomes owner/sender of the case • Most recent AER-X reporter can nullify the case but original reporter can not Proposed change: Harmonization between EVVET 3 business rules and this GPV should be made in terms of follow-up and duplicate identification processes.	
468-475		Comment: Is only the VeDDRA terminology meant here? If yes, this is not qualified for duplicate detection, as it is too varying. The duplicate detection algorithm should also rely on fields containing occur country, primary source country, species, maybe breed, suspect drug(s) and event start date (year, month).	Not accepted. Standard terminology is not only VeDDRA terminology, it may also include e.g. occurrence country, primary source country, species and breed. Additionally, other information such as suspect drug(s) and event start date (year, month) will be used by the duplicate detection algorithm.
481-499	1	Comment: The first paragraph is indicated to be specific to MAHs (line 482), and the last paragraph (lines 498-499) suggests that NCAs are not expected to actively follow up on cases. However, lines 494-497 indicate that in general suspected adverse event reports should be followed up on. To ensure good quality data in EVVET, these follow up requirements	Accepted. The guideline was amended accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		should apply for all suspected adverse event reports, regardless of if MAHs or NCAs received them.	
485	2	Comment: Proposed change (if any): … any additional investigations (e.g. ~~autopsy~~**necropsy**, laboratory…	Accepted. The guideline was amended accordingly.
516-521	1	Comment: It would be good to have clarity on examples of what new information should NOT be submitted as a follow-up. What about corrections in various data fields if they were incorrect in the initial submission (e.g., dates of administration) or unknown in the initial submission and now known (e.g., age of the patient is updated)? What is the postcode is updated as that would help identify duplicates?	Accepted. The text "The sending organisation should record a follow-up report in the Union pharmacovigilance database when significant new information has been received. Significant new information relates e.g. to new suspected adverse event(s) and any new or updated information on the case that may impact on its interpretation. As an example, situations where there is inclusion or exclusion of a clinical sign(s) from the list of medically important VeDDRA terms should be considered as significant changes and thus be recorded in the Union pharmacovigilance database as follow-up reports" was deleted in the guideline.
585	2	Comment: Proposed change (if any): … in the ~~dose~~ **posology** details…	Not accepted. The Union pharmacovigilance database includes the section "Dose per administration".
592-594	1	Comment: This is a change in approach to these cases compared to current practice as described in Volume 9B section 4.4.3. The Volume 9B guidance makes sense, where this new guidance requires number of animals reacting or died could be higher as the number of animals treated.	Partially accepted. The guideline was amended to provide more clarity.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		It also indicates that the parent should still be included in the number of affected animals, even if there was no adverse event observed in the parent. Proposed change: Please maintain guidance from Volume 9B for these cases.	
647-662	1	Comment: Article 73(2) of Regulation 2019/6 only covers: 'Any unfavourable and unintended reaction in any animal to a veterinary medicinal product' and 'any noxious reaction in humans exposed to a veterinary medicinal product' As animal cases without occurrence of suspected adverse events, including asymptomatic human exposure, do not meet those criteria, it is not covered by the legal requirements for adverse event data collection. It should therefore definitely not be required to include these types of reports in the signal management process. How do cases with no suspected adverse events associated with it even indicate a potential risk? They actually indicate there is no risk with the off-label use of the product! This seems to extend the scope of pharmacovigilance, outside the legal definition of pharmacovigilance. Proposed change: This section should be removed. Alternatively, it needs to at least be amended to not	Not accepted. This is in agreement with the definition of pharmacovigilance (Article 14(30) of Regulation (EU) 2019/6).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		be a requirement: Following modification is suggested: 'Where such cases are reported to marketing authorisation holders and may have safety implications with a potential impact on the benefit-risk balance of the concerned veterinary medicinal product(s), the marketing authorisation holders **are recommended to ~~should~~** include them **~~for discussion~~** in the**ir ~~annual statement of the~~** signal management process **~~outcome~~**.'	
674-681	1	Comment: The difference between Misuse and Abuse seems to be vague and is likely to result in inconsistencies. The field of human pharmacoepidemiology is moving away from using the term 'abuse', as that is not considered a very clear term. Proposed change: Removal of the use of the term 'Abuse'.	Accepted. The term "abuse" and its definition have been both deleted in the guideline. The definition for 'misuse' has been amended in the guideline to apply for both animals and humans.
682-686	2	Comment: Make reference to 'inadvertent doping' as part of the accidental exposure to a medicinal product that needs to be reported. Proposed change (if any): 'Accidental exposure', **including 'inadvertent doping'** should be …	Not accepted. The term "accidental exposure" already covers these cases, whenever adverse events are identified. Further explanation may be recorded in the case narrative.
682 ff.	3	Comment:	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The consumption of (drinking) water contaminated with residues of VMPs may also be regarded as "accidental exposure". Contamination of water may occur via e.g. spreading of manure onto agricultural soil and subsequent leaching of (active) substances into groundwater or runoff to surface water, which is used as raw water for the production of drinking water. In this context, we would like to point out that, for example, Chapter 2.6 mentions the potential risks for adverse events in humans as a result of exposure via the environment. Therefore, occurrence of the active ingredient in environmental compartments and drinking water needs to be collected during the literature report to receive information on any potential exposure of humans via the environment. Proposed change (if any): Please add "or the use of contaminated water" in the following sentence: "Accidental exposure relates to situations of unintended exposure of an animal or a human to a medicinal product e.g. accidental ingestion ***or the use of contaminated water."***	The use of contaminated water is covered by the definition of environmental incidents.