18 November 2021
EMA/367359/2021
Veterinary Medicines Division

Overview of comments received on 'Guideline on veterinary good pharmacovigilance practices (VGVP)' (EMA/399713/2020)

Module: Signal Management

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	European Group for Generic Veterinary Products (EGGVP)

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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. It seems that a definition of "Signal" is missing in this module. A definition should be provided or at least a link to the glossary should be made.	Accepted. The definition of signal has been added to the document with further information.
2	FVE welcomes the EMA proposal on a guideline that will ensure appropriate signal management and ensure an efficient pharmacovigilance alert in case of adverse events coming from the use of veterinary medicinal products. We particularly appreciate that this module is applicable to authorised veterinary medicinal products in the EU irrespective of the way of their way of administration and thus considering also adverse event observed when a product is used out of the terms of marketing authorisation (i.e. off-label). We also support that this guideline is also relevant for the authorised homeopathic products.	Acknowledged. No action needed.

3	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. In general, the guideline is clear and well written, the changes performed since the initial draft EGGVP had access to allow today a better understanding of the guideline, and irrelevant or redundant information has been removed which make the text more comprehensible. It is acknowledged that a signal detection yearly report should be generated by the MAH even if no signals are detected. In this regard, and so as to overcome the problem of excessive and unnecessary burden, EGGVP would like to make a proposal that for products with no adverse reactions reported in one year, a simple report form of the signal management process can be sent (i.e. simple declaration - not full management process). For products with no adverse reactions reported in one year, an exemption to review all important medical terms should be accepted (it has no value to monitor these expressions in case of no adverse events reported). While this seems to be implicit in the guideline, EGGVP is missing a clear reference and mention that indeed a simple declaration or statement would be acceptable. The provision of sales data and incidence calculations in the new Union databases is an area of major concern for MAHs as it may lead to substantial and additional work for MAHs. As Section 3.3 in this draft guideline is still under development, the final provisions are still unknown.	For products with no adverse events reported in the last year or with no sales, by the due date, the MAH has to submit annually two statements, one confirming that the overall benefit-risk balanced is unchanged, and one confirming that the signal management procedure has been conducted in compliance with the pharmacovigilance guidelines published by the Agency (VGVP). This is in line with Article 19(1) from the Commission Implementing Regulation (EU) 2021/1281. The submission of these statements will be made as simple as possible in the Union pharmacovigilance database. Article 55 requires the submission of sales data independently of adverse reactions reported throughout the year.

	EGGVP hopes that Section 3.3 in preparation will clarify how MAHs shall calculate "number of animals treated". Solutions should be envisaged so that any additional burden is minimised. An automated process for calculation of the estimated number of animal treated would be a good solution. The MAH shall provide the percentage of animal species treated and the total dose by species only once, e.g. at the first DLP. As the sales data are in the UPD, the number of animals treated shall be calculated by the system. Clarification where is this submitted is critical. EGGVP understand submission is in UPD only to avoid duplication of submissions. Furthermore, an incidence calculation query shall be included in the EVVet 3. Last but not least, it should be noted that the only utility of providing data / treated animals for incidence calculations in case of adverse reactions is to assess the incidence. Therefore competent authorities should consider that if there are no adverse reactions, it should not be necessary to provide these data. If this is agreed, we would be thankful if clear mention in the guidance could be made that if there are no adverse reports for a certain product, MAH may skip the treated animals calculations and submission in the database, Otherwise this will involve a waste of resources and unnecessary burden. This is an important aspect for MAHs. As signal management activities are new for marketing authorization holders, many questions on details and request for examples are popping up. It is acknowledged that this guideline may not be the appropriate tool to provide a response to this demand. Therefore it is suggested that additional support is provided separately and later on i.e. by developing a Q&A document (references under the "specific comments" section).	

2. Specific comments on text

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
85-90	3	Comment: The process for triggering a variation is not very clear in this paragraph but it is described under section 2.6 and 3 (figure 2). Reference to these sections would be useful in this paragraph. Proposal: *"Where the outcome of the signal management process identifies a change to the benefit-risk balance, a new risk, the marketing authorisation holder shall notify it without delay and no later than 30 calendar days, of receipt of the suspected adverse event report, to competent authorities, and where necessary submit a variation to the terms of the marketing authorisation in accordance with Articles 77(10) and 81(2) of Regulation (EU) 2019/6* ***(see Section 2.6 and Section 3 – figure 2)."***	Regulatory process involving variations will be clarified.
86-88	1	Comment: The comma at the end of line 86 should be replaced by 'or'. The delay of 30 days is not clear. Is it from the validation of the signal or from the "receipt of suspected AE report"? This addition seems incorrect, as a change in the benefit risk will in most cases not be related to one suspected adverse event report. The	Accepted. Regarding the 30 days, indeed this refers to the identification of the change to the benefit-risk balance or a new risk.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		30-day clock start should be related to the identification of the change to the benefit risk balance. Proposed change: Please modify the sentence to read: "Where the outcome of the signal management process identifies a change to the benefit-risk balance~~,~~ **or** a new risk, the marketing authorisation holder shall notify it without delay and no later than 30 calendar days, of **the identification of the change to the benefit risk balance** ~~**receipt of the suspected adverse event report**~~, to competent authorities"	
91-96	1	Comment: There seems to be a duplication of wording in this sentence. Proposed change : Please modify the sentence to read: "In case of an impact on the benefit-risk balance of the veterinary medicinal product concerned, on animal or public health, or on protection of the environment that is considered an emerging safety issue, identified by the marketing authorisation holder according to Article 58(10) of the Regulation, the marketing authorisation holder should notify it to the relevant competent authority(ies) without delay and no later than 3 working days following the identification ~~**of an emerging safety issue by the marketing authorisation holder**~~ (see section 2.3.1)."	Accepted.
92- 121	2	Comment:	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): …animal **health and welfare** or…	
97-98	1	Comment: It would be highly appreciated, if definitions and examples for the various steps (signal detection, prioritisation, validation, assessment and recommendation for action) can be provided.	Partly accepted. Definition of signal detection will be added in the annex. Additional definitions are not considered necessary for other activities given the information provided already in the guidelines.
95 & 133 & 148 & 345	1	Comment: Inconsistency in timeline for reporting ESIs (3 working days in lines 95 & 345 and 3 calendar days in line 133 & 148). The timeline should be consistent. Proposed change: Please update lines 133 & 148 to indicate **3 working days**	Accepted.
103	2	Comment: Proposed change (if any): … including all **open source** scientific information…	Not accepted. Unpublished data can be the source of a signal. Furthermore, if there is any relevant publication in the scientific literature, whether open source or not, the MAH is expected to make sufficient efforts to access that information and take it into account in the benefit-risk assessment of their products, including during the signal management process.
106	1	Comment: What is a pharmacovigilance profile? Is this meant to be the safety profile of a veterinary medicinal product? If not, please provide a definition.	Accepted. Clarification added in the text.
106	2	Comment:	Not accepted.

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		Proposed change (if any): … scientific literature **databases**. Marketing…	
136-140	1	Comment: "Restriction of use": Does this also includes a specific batch recall? Please clarify.	Yes, in some cases, emerging safety issues or signals may concern a quality issue and specific batch recalls may be necessary. However, a batch recall on itself is not considered an emerging safety issue.
136	2	Comment: Proposed change (if any): … published in the **peer-reviewed** scientific literature…	Not accepted. Because of a precautionary principal, potential emerging safety issues should be considered from any data.
141-142	1	Comment: Clarification is requested on how animal health companies are expected to assess seriousness in humans (e.g. requiring hospitalization) - solely from data provided in the case report (patient was/was not hospitalized). In a significant number of cases the information provided may not be sufficient, especially considering that animal health companies do not typically have the expertise internally, or access to medical doctors, to do these assessments.	This sentence has been deleted from the guideline.

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Footnote on page 6	1	Comment: Footnote: 'Reporting Odds Ratio (ROR) is a statistical measure based on the odds observed for an event occurring with a particular product compared to the odds observed of that same event in a reference data set of products.' It would be highly valued to receive the criteria for the reference data set for all products (e.g., same therapeutic class or all approved products for a species).	The reference data set usually applies to all other products on the database. There is a specific dashboard that allows you to change the criteria for the reference data set to be all products of the same therapeutic class.
167-171	1	Comment: This section trying to describe use of MI terms is confusing with conflicting guidance. Sentence in lines 164-166 indicating that MI terms are intended for signal prioritisation is sufficient. Proposed change: Please delete lines 167-171.	Not accepted. This will be further clarified in the training sessions.
169-171	3	Comment: This section reads a bit complicated and almost contradictory. What is according to this guideline considered as "exceptional circumstances"? Further clarification required, possibly to be developed via Q&A separately (see general comments).	Partly accepted. Wording has been changed and clarification has been added next to the definition of a signal. Based on experience gained in pharmacovigilance, it is known that one singe well-documented case has led to regulatory actions such as updating the product information of a veterinary medicinal product. However, this is not a common situation.
178	2	Comment: Proposed change (if any): … on new **drug** associations…	Not accepted.

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182	1	Comment: Definition of seriousness is missing in VGPV glossary. Or is the VICH definition to be implicitly considered? Clarity is sought regarding what is meant here with seriousness; serious vs. non-serious is not used in Reg. 2019/6 anymore.	VICH definition of seriousness if implicitly considered.
187	3	Comment: Some examples of species-specific events would be welcome. These can be developed via Q&A separately (see general comments). Proposal: • Species-specific events (e.g. <explanation or an example>)	Please see MI term list.
194-196	3	Comment: Training or guidance on the possibilities for grouping - and how MAHs can demonstrate so - would be welcome. This can be developed via Q&A separately (see general comments).	Accepted. This is still under development and will be clarified.
201-204	1	Comment: Clarification is requested to indicate if it is required for a MAH to make use of the available pre-defined queries in the Union PhV Database. It would be appreciated, if the pre-defined query parameters can be shared.	Pre-defined queries will be available in the Union pharmacovigilance database and the MAHs are expected to use the queries at least once a year before the due date.

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203	1	Comment: For small and medium-sized MAHs with low numbers of AEs per product / product group, ROR will not lead to the most relevant signals. What other query options do they have? Especially small and medium-sized MAHs will not have their own AE database with extensive signal detection options (they use e.g. an Excel-file).	Disproportionality methods should be applied to databases of appropriate size and background. The use of disproportionality methods, including the ROR, is not appropriate in all situations. Application of disproportionality methods to a dataset that is too small or with a limited set of products or events reported might not be relevant and provides no added benefits compared to using qualitative methods and simple quantitative methods. Therefore, it may be more appropriate for small databases to apply qualitative methods or simple rule-based methods (e.g. count of case reports) or a combination of these. Access will be provided to perform signal management directly in the Union pharmacovigilance database and take advantage from the full dataset. This will be clarified during the training sessions.
212	1	Comment: "Outputs generated on a product basis": for the MAH will that be done for one specific trade name or will we be able to select several trade Names for same/similar products? Please clarify.	MAHs will be able to select several trade names and group them if necessary. Further guidance will be provided.
213-214	1	Comment: Does this include the use of the MAHs own PV databases? Please clarify.	Yes, this refers to the use of the MAH's own database.
224	1	Comment: The check if the AE occurred after exposure to the VMP is already done at the time of case entry.	This is acknowledged.

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		This is therefore (nearly) always true, so this is not a strong selection criterium.	
225	1	Comment: All stakeholders strive to avoid duplicates in the database, so the number of duplicates is (hopefully) low. Then this is not a strong selection criterium.	This is acknowledged.
240-243	1	Comment: The MAH would appreciate a lower time limit for older products or maximum number of cases for review due to data access limitations and the more current cases containing the more relevant information.	Not accepted. Relevant cases should not be excluded if available in the database.
246	2	Comment: Proposed change (if any): … outcome, e.g. **peer-reviewed** literature review…	Not accepted.
252-255	1	Comment: This bullet point should be listed under the step 'validation'.	Not accepted. The signal validation step in veterinary is a simple first step. The total number of supporting cases will have an impact on the final conclusion about the potential causal association between the veterinary medicinal product and the event.
254	1	Comment: Clarification is sought on what is meant with health care professional. Is it a Medical Doctor in cases where the AE occurred in a human being after contact with a VMP? Or is an 'ANIMAL health care	Indeed, this could be the medical doctor in case of human adverse events for example, and animal healthcare professional following the definition provided in the annex.

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		professional' according to the definition given in the Glossary meant here?	
256	1	Comment: Incidence is already listed under signal detection parameters (line 109) and should be part of validation if not used for detection (but not assessment).	Not accepted. The signal validation step in veterinary is a simple first step. The incidence is additional relevant information which can help reaching a final conclusion on the potential causal association between the product/active substance and the event.
261	1	Comment: Quality of the data and their supporting documentation seems to better fit under validation instead of the assessment step.	Not accepted. The signal validation step in veterinary is a simple first step. Quality of the data of the supportive cases is additional relevant information which can help reaching a final conclusion on the potential causal association between the product/active substance and the event.
264	1	Comment: Disproportionality of reporting seems to better be listed under validation.	Not accepted. The signal validation step in veterinary is a simple first step. Disproportionality of reporting is additional relevant information which can help reaching a final conclusion on the potential causal association between the product/active substance and the event
269	2	Comment: Proposed change (if any): … cases in the **peer-reviewed** literature review…	Not accepted.
277	1	Comment: Typo: the last word of this line ('it') should be removed.	Accepted.

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		Proposed change: Please modify to read: "... if ~~it~~ this adverse event..."	
287-288	1	Comment: It should be clarified, if the need to notify within 30 calendar days does only apply to medically important terms (figure 2 seems to suggest this).	Accepted. Figure 2 will be amended.
304	1	Comment: Still lacking detail on PASS and authorities expectations here. Please provide confirmation that this guidance is being drafted.	This is in the work plan for 2022 and more details will be provided.
316	1	Comment: Figure 2: Is the lowest action line in the figure ('AEs and one or several signals assessed not requiring 3-Day or 30-Day notification') referring to refuted signals? If so, please clarify this in the figure. Proposed change: Please modify figure 2 to indicate that the 30 calendar day notification is only applicable for signals involving MI terms.	Not accepted. This has been amended in the document and figure 2. The amended version mentions that the 30 day notification requirement concerns signals for which a change to the benefit-risk or a new risk has been identified (and therefore there are proposals for further regulatory action), irrespective of the signal concerning MI terms or other VeDDRA terms.
333-336	1	Comment: This description is very vague. Who determines due dates? Where, in what form and when will those due dates be published? According to VGVP Module 'Collection and recording of suspected AEs for VMPs', literature review shall be performed prior to the due date of the signal management procedure to ensure that any AE reports are recorded in the Union pharmacovigilance database. So due dates should be	Further clarification will be provided regarding the due dates.

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		available at least 60 days prior the annual literature review would be performed.	
333-336	3	Comment: For clarification: in case of products with more than one active substance, which date will apply, if different? Proposal: Text addition – ***"In cases where there may be any conflicts or questions on which is the applicable due date (i.e. products with more than one active substance), this should be discussed and agreed between the MAH and the concerned competent authority".***	Further clarification will be provided regarding the due dates.
340	1	Comment: What is the period referred to in line 340? There will be a due date set for submission of the annual statement, but if the MAH needs to prepare this document, the document cannot cover the period until the due date, as there will be time needed to prepare the document and review it according to the QMS. There should therefore also be a reporting period defined, with a data lock point.	This refers to the annual period (i.e. in the last year). The idea is not to generate a new report by the time of the due date, but to submit the signals involving MI terms that have been reviewed throughout the year with no proposals for regulatory action. However, these signals can be submitted at any time throughout the year (by the due date at the latest). Signal detection analyses in the Union pharmacovigilance database should be performed at least once per year and this should be done within 2 months before the due dates.
349	1	Comment: Section on signal reporting seems contradicting to figure 2. We read figure 2 as only	Accepted. Figure has been updated. The amended version mentions that the 30-day notification requirement concerns

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		signals with Mi term requires 30-days notification in case of change to B/R. However, section 3.2.1. that signal where MAH identifies a change to B-R should be notified. Text in section 3.2.1 is the intention and the diagram requires adaptation.	signals for which a change to the benefit-risk or a new risk has been identified (and therefore there are proposals for further regulatory action), irrespective of the signal concerning MI terms or other VeDDRA terms.
359	1	Comment: Clarification is requested as to what information should be included in the line listing referred to. However, it is AnimalhealthEurope understanding that the reference to a separate 'line listing' is unnecessary since the Agency already, inevitably, will have all the cases. This should be changed to refer to case numbers only. Proposed change: Please modify to read: " …cases **numbers …** attached as line listing…"	Accepted. The guideline will be amended accordingly.
358-362	1	Comment: Clarification is requested which VeDDRA Preferred Terms should be entered. It is assumed that only cases supporting the signal and that were assessed during signal management activities should be entered. Clarification is also requested as to whether this bullet point is restricted to validated signals.	The VeDDRA terms concerned in the signal. Further guidance will be provided on the actual assessment and inclusion of relevant cases for the signal (template assessment report). Non-validated signals should not be entered in the Union pharmacovigilance database.
360-361 & 383-384	1	Comment: It would be helpful for MAHs to receive more detailed information on the format and content of these signal assessment reports referred to.	This will be clarified. A template assessment report will be provided.

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366	1	Comment: "statement for each VMP for which the MAH is responsible". This should not be at the trade name level.	Accepted. Grouping will be allowed on the basis of same or similar products.
375-376	1	Comment: Regarding recording signals involving MI terms, it should be clear that only validated signals are recorded in Union Pharmacovigilance database as described in lines 234-236. Proposed change: Please add "valid" to read, "… any other **valid** signals involving MI terms…".	Accepted. This will be made clear.
363-387	1	Comments: 1) How does the reporting look like, when no signal was detected (due to missing AE reports or not validated signals)? Figure 2 only says 'simple statement'. Which data have to be entered in which fields? 2) How does the reporting look like when the signal management process was performed by grouping (see lines 194-196)? Is it possible to perform one annual reporting (meaning one entry for fields administrative information, entry identified as 'yearly signal management' and due date as well as per signal) for a group of VMPs to reduce administrative burden?	1) In case of no signals detected throughout the year, the only requirement would be to submit the statements on benefit-risk balance and that the signal management procedure has been conducted according to the guidelines published by the Agency. 2) More information about the grouping will be provided during the training sessions. The systems are being developed in the view of allowing grouping and reducing administrative burden.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
371-444	3	Comment: It is acknowledged that a signal detection yearly report should be generated by the MAH even if no signals are detected. In this regard, and so as to overcome the problem of excessive and unnecessary burden, EGGVP would like to make a proposal that for products with no adverse reactions reported in one year, a simple report form of the signal management process can be sent (i.e. simple declaration - not full management process). For products with no adverse reactions reported in one year, an exemption to review all important medical terms should be accepted (it has no value to monitor these expressions in case of no adverse events reported) Proposal: Removal in 371 – ~~"This should be done regardless of any signals detected throughout the year."~~ Addition after 444- ***"If no signal was detected or validated: a standard statement confirming that the signal management process has been conducted in line with the published relevant guidance in this Module should be included. A statement confirming that the benefit-risk balance of the concerned veterinary medicinal product should also be included"***	Accepted. No signal detection yearly report should be generated by the MAH when no signals are detected. In case of no signals detected throughout the year, the only requirement would be to submit the statement on benefit-risk balance and the statement to confirm that the signal management process has been conducting in line with the relevant guidelines published by the Agency. For products with no adverse events reported throughout the year, there is no need to review MI terms.

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381-384	1	Comment: this bullet point seems to suggest that every signal that did not require reporting within 30 days still has to be entered separately in the Union PhV Database. Having the option to include these in one report with only one associated entry would avoid a potential increase in administrative burden. As it is currently still unclear what the capabilities of the PV related IT tools are, this is causing concerns.	For the annual submission, assessed signals that have been reviewed throughout the year but without proposals for regulatory action should be entered in the Union PhV database by the due date at the latest. A brief summary of the review of the cases and the conclusion on the assessment (either proposing to refute the signal or close monitoring) should be included. The capabilities of the system will be shown during the training session.
388	1	Comment: There is no section relating to '3.3 Incidence reporting by marketing authorisation' and due to the requirements of EU 2019/06 the Agency has the relevant sales data to generate / check incidence rates. In addition, based on the existing and new QRD (v 9.0), MAH will inevitably have to propose incidence rates for any adverse event sign to be included in the SPC. This section is therefore redundant. Proposed change: Please delete line 388 and renumber following sections accordingly.	This will be updated.
399-340	3	Comment: It is uncertain if the list of due dates would apply to veterinary medicinal products authorised in the EU by national procedures. For APIs where no DLPs were set for the PSUR in the past, will new due dates	The due dates will apply to all veterinary medicinal products authorised in the EU, including those authorised by national procedures (MRP, DCP, NAP).

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		be set? And will these dates be set by the EMA? (i.e. mineral vitamins). Clarification would be welcome.	EMA will publish a list with the defined due dates and more information on this.
402-410	1	Comment: As competent authorities are also involved in signal management activities; these requirements should apply to both MAHs and competent authorities.	Not accepted. This section is focused on the requirements for MAHs.
402-403	3	Comment: Marketing authorisation holders should make sure to document their signal management process; in this regard details and examples on which documents should be present for inspection would be welcome. Further clarification required, possibly to be developed via Q&A separately (see general comments).	We cannot list all the documents requested during inspections as there could be the risk that we miss something. Further details might be provided at a Q&A document.
411	3	Comment: Could further details about such a tracking system, which can be used by MAHs and competent authorities, be provided? Are the dates of signal detection and final report entered into EVVet 3. Might there be a possibility to take a listing of time data out of the system to be presented for inspection? As the text reads now, it is not clear what will be requested by authorities to MAHs during inspection to prove the requirements are met. If there would be recommendations on the exact pieces of	Further details might be provided at a Q&A document. This tracking system is not purely part of the QMS, it's a tool to proof the signal management activities carried out by the MAH. The inspectors, in addition to the description of the signal management process, could ask for any evidence regarding signal management activities. However, we cannot list all the documents requested during inspections as there could be the risk that we miss something.

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		documentation that should be extracted for inspection that would be very welcome.	
440-441	1	Comment: Please clarify if ALL symptomatic human exposures are automatically prioritized, or symptomatic human exposures related to a specific signal?	The text has been amended. All events that occur in humans **associated with the exposure to a veterinary medicinal product are considered part of the MI terms list and** should be prioritised.
447	1	Comment: MAHs continue to be concerned about the practical implications of the Medically Important Terms list. While it is understood that this is an approach which is used on the human side, in practice for an MAH with a range of companion animal vaccines / antiparasitics or non-steroidal anti-inflammatories, it means that as well as the continual monitoring of the BR as required by the regulation, there is going to be additional obligations on a weekly / monthly basis for all these products based on the MIT list but in most cases the issues are going to already be covered by the SPC and as such will create an separate non-value added administrative burden. MAH would recommend that this list is very much more limited in scope until both the Agency / NCAs and MAHs have greater experience in managing it AND the new systems and	Not accepted. Signals concerning terms that are already sufficiently reflected in the SmPC will not lead to validated signals (see guidance). The list is already a very succinct compact list compared to the relevant list in human side of important medical events list (7274 events) and designated medical events list (62 events). As more experience is gained with the signal management procedure and the MI terms list, it will be updated accordingly.

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		processes (which are still not finalised either) – which is already creating incredible stress on MAHs – and likely the Agency / NCAs alike. Proposed change: Reduce the number of terms in this list and phase in over the following years once the system is functioning for both MAH and the Agency/NCAs.	
447	2	Comment: Please insert explanation for NOS abbreviation, i.e. NOS = Adverse effects not elsewhere classified Proposed change (if any):	Accepted.