EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

29 May 2020
EMA/CVMP/111028/2020
Committee for Medicinal Products for Veterinary Use

Scientific recommendations for implementing measures under Article 77(6) of Regulation (EU) 2019/6 on veterinary medicinal products regarding good pharmacovigilance practice

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Introduction

On 6 February 2019 the European Commission sent a request to the European Medicines Agency for scientific recommendations on good pharmacovigilance practices, taking into account the following:

- the experience gained with the application of the current veterinary pharmacovigilance system as established in Volume 9B of The Rules Governing Medicinal Products in the European Union - Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use;
- the signal management process defined in Article 4, provided for in Article 81 and outlined in Recital 63 of Regulation 2019/6;
- the experience gained with the human signal management process as laid down in Commission Implementing Regulation (EU) No 520/2012 and their guidelines on good pharmacovigilance practices (GVP);
- the responsibilities of marketing authorisation holders as referred to in Articles 58 and 77 and his qualified person responsible for pharmacovigilance as well as rules for communication;
- the responsibilities of competent authorities as referred to in Articles 79 and 81(3-6) as well as rules for communication;
- reporting and recording of suspected adverse events as referred to in Article 76 as the necessary requirements for a smooth working of the pharmacovigilance data base and an effective signal management process;
- calculation of incidence of suspected adverse events given in the database according to Article 75(3); and
- the specific rules on pharmacovigilance inspections referred to Article 126.

The Committee for Medicinal Products for Veterinary Use (CVMP) formed three expert groups to prepare the scientific recommendations: one group concerning reporting and recording of adverse events and the signal management process, one group on inspections of pharmacovigilance systems for veterinary medicinal products and one group on pharmacovigilance communications.

The expert group on reporting and recording of adverse events and the signal management process was composed of five experts selected from the European network of experts, on the basis of recommendations from the national competent authorities, and two Agency staff members with expertise on veterinary pharmacovigilance.

The expert group on inspections of pharmacovigilance systems for veterinary medicinal products was composed of four experts selected from the European network of experts, on the basis of recommendations from the national competent authorities, and two Agency staff members with expertise on veterinary pharmacovigilance inspections.

The expert group on pharmacovigilance communication was composed of three experts selected from the European network of experts, on the basis of recommendations from the national competent authorities, and two Agency staff members with expertise on veterinary pharmacovigilance and communication.

In view of the applicability of the pharmacovigilance system to all products authorised in the EU independent of the route of authorisation, the responsibilities of the competent authorities regarding pharmacovigilance and their responsibilities regarding pharmacovigilance inspections, it was

considered appropriate to consult the Coordination group for Mutual recognition and Decentralised procedures (veterinary), CMDv.

The expert groups submitted their draft recommendations to the CMDv and CVMP on 18 March 2020 and 19 March 2020, respectively.

The CMDv endorsed the recommendations on 24 April 2020 and the CVMP adopted the advice on 21 May 2020.

Considerations and rationale for the recommendations

Regulation (EU) 2019/6 aims to reduce the administrative burden, enhance the internal market and increase the availability of veterinary medicinal products, while guaranteeing a high level of public and animal health and environmental protection.

The recommendations made in this advice reflect the general principles and key factors for good pharmacovigilance practice to ensure a robust and efficient pharmacovigilance system, that will rely on the tool of signal management. These general principles and key factors will need to be complemented by guidelines addressing the specific details required for full and appropriate implementation of the legal requirements while ensuring a system that is adaptable and flexible to the needs of all stakeholders and that can be readily updated in light of experience gained. The recommendations made in this advice take into account the experience gained from the implementation of similar legislation relating to human pharmacovigilance [Implementing Regulation (EU) No 520/2012], where the principal lesson learned was the necessity to ensure flexibility within the pharmacovigilance system. For the purposes of the scientific recommendations in this document, specific reference to VICH guidelines is not made throughout the text, as inherently all adopted VICH guidelines compliant with Regulation (EU) 2019/6 are applicable at EU level. The application of the recommendations for pharmacovigilance detailed in this document, which will be supplemented by guidance, will enable the primary objectives of the new legislation to be achieved, principally the reduction of administrative burden while ensuring a high level of protection for animal and public health and the environment.

Overview of recommendations

The recommendations for good veterinary pharmacovigilance practice set out in this advice relate to the following pharmacovigilance activities: adverse event recording and reporting, provision of data for calculation of incidence of reported adverse events, signal management, pharmacovigilance communication and pharmacovigilance inspections.

Adverse event reporting remains the primary information source for post-authorisation safety monitoring and provides most of the data for the evaluation of the benefit-risk profile of a product when marketed. Under the current legislative requirement, marketing authorisation holders report adverse events to the competent authority in the country where the event occurred. The competent authorities, in turn, have an important role in quality control of adverse event data before submitting the report into the EU pharmacovigilance database. Regulation (EU) 2019/6 changes the reporting route for marketing authorisation holders who will in future submit adverse event reports directly into the Union pharmacovigilance database. This has potential implications for data quality, as competent authorities will no longer have a data quality control function for reports submitted by marketing authorisation holders into the Union pharmacovigilance database. It will be fundamental for both marketing authorisation holders and competent authorities to implement measures that ensure submission of good quality adverse event reports which are as complete as possible to the Union pharmacovigilance database.

Adverse event data are collected in the Union pharmacovigilance database, a system that enables analysis of information received over the full life-cycle of a product. Marketing authorisation holders are required to continuously monitor the benefit-risk balance of their products on the basis of these data, and standardised queries will be available for them to access and analyse the data directly in the Union pharmacovigilance database. Most pharmacovigilance data are observational, and a relative comparison across the full dataset of the Union pharmacovigilance database will be useful to help identify potential signals for further investigation. In order to facilitate appropriate use of resources and reduce administrative burden, it is recognised that there will be a need to develop guidance to supplement the recommendations in this document. The purpose of such guidance will be to enable prioritisation of products for data analysis, focussing on those that are new to the marketplace, or those with uncertain safety profile, or those that could be expected to pose a risk to animal health, public health or the environment. Key elements considered relevant for the risk-based approach are mentioned in the recommendations and include the type of product, the length of time on the market, the stability of the pharmacovigilance profile of the product(s) or the active substance(s) and the relative severity of the adverse event reported. In addition, a list of medically important VeDDRA terms will be established. This list will be used to focus on reports of adverse events that deserve special attention, irrespective of other criteria used to prioritise safety evaluation.

Marketing authorisation holders will be expected to perform their signal management activities in line with the risk-based approach outlined in guidance to be developed, and, where mitigation actions are deemed necessary in view of any change to the benefit-risk balance of the product, to instigate appropriate actions in accordance with Article 81(2) of Regulation (EU) 2019/6. Furthermore, marketing authorisation holders will be required to record in the Union pharmacovigilance database, at least annually, the results and outcomes of the signal management process, including a conclusion on the benefit-risk balance. Hence, for products for which sufficient market experience is available and with a pharmacovigilance profile considered stable, it is anticipated that the workload for marketing authorisation holders will be limited to the normal activities of processing and evaluating the adverse event reports received, monitoring for new risks in line with the risk-based approach and recording the results and outcomes of the analysis related to new risks, when necessary, in the Union pharmacovigilance database, including a conclusion on the benefit risk-balance on an annual basis.

Similar to the risk-based approach recommended for the prioritisation of marketing authorisation holders' signal management activities, it is recommended that a risk-based approach be developed to enable prioritisation of surveillance activities by competent authorities and the Agency, in particular for determining the frequency and extent of data analysis required for specific products or groups of products. The surveillance activities of the competent authorities and the Agency will relate to either the evaluation of the results and outcomes of the marketing authorisation holder's signal management process recorded in the Union pharmacovigilance database (as required in accordance with Article 79(1)) or a more targeted signal management process (as foreseen in Article 81(3)). Furthermore, it is recommended that work-share procedures are set-up between the competent authorities with a view to reducing administrative burden and avoiding duplication of surveillance activities. The work-share is expected to be organised on the basis of products grouped by active substance, which is anticipated to strengthen the power of the analysis and ensure consistency of approach to data analysis for similar products.

To evaluate compliance with the legislative requirements and relevant guidelines, inspections of marketing authorisation holders' pharmacovigilance systems will take place at appropriate intervals, as required by Article 126(1) of Regulation (EU) 2019/6. It is recommended that such inspections be conducted based on risks specific to the respective veterinary medicinal products or the inspected party, and that this work will be coordinated, with a view to promoting work-sharing and avoiding duplication of inspections of pharmacovigilance systems. The approach to the coordination of this

activity and procedures for work-sharing for competent authorities will be developed in specific guidance. The pharmacovigilance system master file that allows marketing authorisation holders to describe in detail, in one document, their system for collecting, collating and evaluating information on adverse events concerning their authorised veterinary medicinal products, will be the primary focus of pharmacovigilance inspections.

According to Article 75(3) of Regulation (EU) 2019/6, the general public shall be provided with access to the number and the incidence of adverse events reported each year, broken down by veterinary medicinal product, animal species and type of adverse event. To facilitate this requirement, it is recommended that marketing authorisation holders provide an estimation of the number of treated animals. It is noted that Article 58(12) of Regulation (EU) 2019/6 also requires the marketing authorisation holders to record in the Union product database the annual volume of sales of each of its veterinary medicinal products.

In relation to pharmacovigilance communication, recommendations are made to ensure that marketing authorisation holders have appropriate processes and procedures in place to communicate any change in safety profile of their products, in particular urgent safety issues, to relevant stakeholders. Similarly, it is recommended that competent authorities and the Agency establish procedures to ensure effective and prompt communication of safety information that could impact on animal or public health or the environment.

In conclusion, it is expected that the application of the recommendations for good pharmacovigilance practice detailed in this document, which will be supplemented by guidance, will enable the primary objectives of the new legislation to be achieved, in particular ensuring a high level of protection for animal and public health and the environment. At the same time, these recommendations aim to reduce unnecessary burden by promoting a risk-based approach to pharmacovigilance activities and enabling work-sharing and consolidation of efforts, where possible.

Requirements proposed for marketing authorisation holders in this advice apply by analogy to registration holders for registered homeopathic veterinary medicinal products (Regulation (EU) 2019/6, Article 87(5)).

Points for further consideration

The recommendations on good pharmacovigilance practice rely on the availability of a fully operational Union pharmacovigilance database and the functional specifications of a fully populated Union product database. In addition, a functional Union pharmacovigilance system is dependent on adequate resourcing within the EU regulatory network as well as by marketing authorisation holders.

Recommendations on measures on good pharmacovigilance practice

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1. Reporting and recording of adverse events and the signal management process

Terminology to describe adverse events

It is noted that various terms are used in Regulation (EU) 2019/6 for an 'adverse event' i.e. 'suspected adverse event', 'adverse event', 'potential serious adverse event' and 'adverse reaction'. For the purposes of this advice the term 'adverse event' (as defined in VICH GL24) is used throughout.

Overview of adverse event reporting

Currently, adverse events are reported in two possible ways in the EU, and in both it is the competent authority that forwards the adverse event report to the current EU pharmacovigilance database – EudraVigilance Veterinary - as follows:

a) The primary source (veterinarian/owner/farmer/healthcare professional etc.) reports an adverse event to the marketing authorisation holder. The marketing authorisation holder then reports this adverse event to the competent authority of the Member State where the adverse event occurred in the EU. The competent authority checks the report for completeness and the database for duplicates; and then submits the adverse event report to EudraVigilance Veterinary. If the marketing authorisation holder receives further information on the reported adverse event this information will be sent as a follow-up to the competent authority who will then submit the information into EudraVigilance Veterinary.

b) The primary source reports an adverse event to the competent authority, which then forwards the adverse event report to the marketing authorisation holder and submits the report to EudraVigilance Veterinary. Any additional information provided by the marketing authorisation holder is sent as a follow-up to the competent authority which updates the adverse event report and submits the updated report to EudraVigilance Veterinary.

Regulation (EU) 2019/6 changes the reporting routes such that the body receiving the adverse event report from the primary source is responsible for submitting this report directly to the Union pharmacovigilance database. Figure 1 shows the flow of information and actions to be taken in line good pharmacovigilance practice under Regulation (EU) 2019/6. The following will apply:

a) The primary source reports an adverse event to the marketing authorisation holder who will then submit the adverse event report to the Union pharmacovigilance database.

b) The primary source reports an adverse event to the competent authority which will then submit the adverse event report to the Union pharmacovigilance database.

The change in reporting routes has the potential to reduce administrative burden. However, to facilitate analysis of the information in the Union pharmacovigilance database, provisions will have to be put in place to ensure good quality and consistency of adverse event data.

For adverse events originating in third countries the reporting routes remain the same as under the current legislation – marketing authorisation holders submit reports directly into the relevant Union level database, currently EudraVigilance Veterinary, in the future the Union pharmacovigilance database.

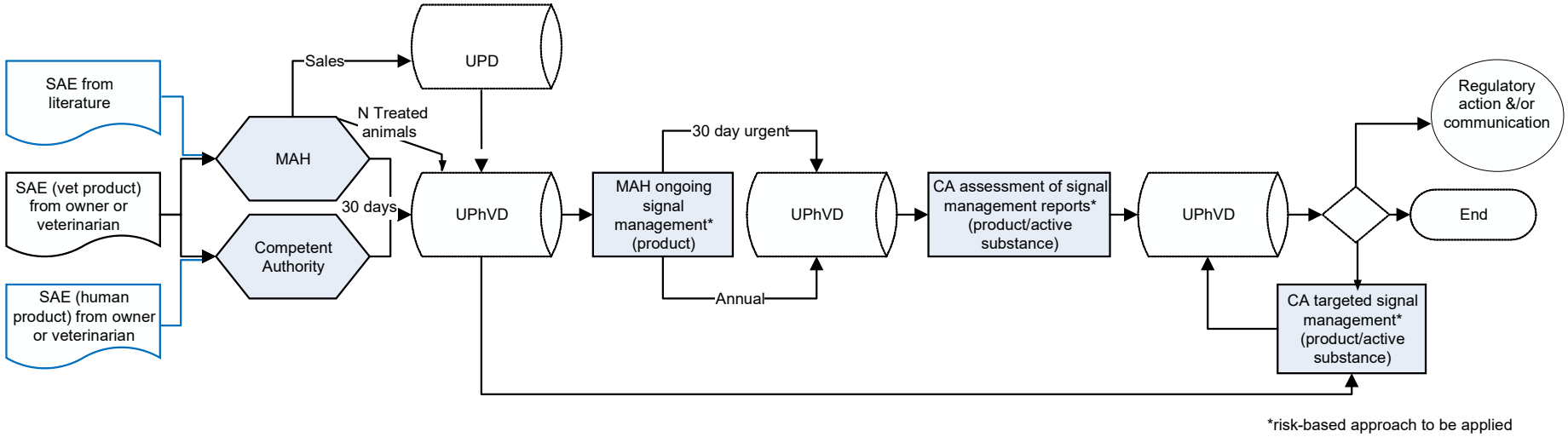

Figure 1. Overview of information flow and adverse event reporting and signal management processes under Regulation (EU) 2019/6

1.1. Reporting and recording of adverse events

1.1.1. Minimum requirements for adverse event reports

Recommendation

An adverse event report shall include at least the following: an identifiable reporter or source (including the country code); details of an identifiable animal(s) or human(s) or environment; veterinary or human medicinal product name(s) and details of the adverse event(s).

Where the name of the product is not included in the initial report, marketing authorisation holders and competent authorities shall make reasonable efforts to obtain the name of the medicinal product concerned. Exceptionally, where (a) specific medicinal product(s) cannot be identified, the name(s) of the active substance(s) shall be reported.

Rationale

To ensure meaningful adverse event reports that enable pharmacovigilance, as defined in Article 4(30), minimum criteria are required for adverse event reporting. The minimum criteria are essential for confirming the validity of the report as an adverse event for the benefit-risk evaluation of the product concerned. Defining the minimum criteria in legislation will ensure that reports contain adequate information to enable evaluation, minimising unnecessary burden on competent authorities or marketing authorisation holders due to erroneously reported events.

The Union pharmacovigilance database will accept adverse events that include one or multiple products. These products may be identified by either the specific medicinal product name, or, where this is not specified, the active substance. It is expected that reasonable efforts are made by marketing authorisation holders and competent authorities to obtain the name(s) of the medicinal product(s) concerned, however, exceptionally, where this information is not available, the name(s) of the active substance shall be submitted.

1.1.2. Veterinary medicinal product names

Recommendation

To enable comprehensive analysis of adverse event data for products authorised under different procedures in different Member States, the marketing authorisation holder shall identify the same or similar products and provide the corresponding product name(s) and authorisation number(s) to the Union pharmacovigilance database.

To enable comprehensive analysis of third country adverse event reports, the marketing authorisation holder shall identify the specific product concerned by the report and provide the corresponding product name(s) and authorisation number(s) of the same or similar EU authorised products to the Union pharmacovigilance database.

Rationale

In line with Article 76(2) of Regulation (EU) 2019/6, marketing authorisation holders shall record in the Union pharmacovigilance database all adverse events reported to them that occurred within the Union or in a third country. A veterinary medicinal product may have different names in third countries compared to EU authorisations, or even different names in different EU Member States. At present, approximately half of the reports in EudraVigilance Veterinary (48%[1]) are from outside the EU and this

[1] Veterinary pharmacovigilance public bulletin 2019

figure is expected to increase in future To be able to retrieve adverse event reports concerning products authorised under different names in third countries or different EU Member States from the Union pharmacovigilance database and enable comprehensive analysis of that pharmacovigilance data, a link needs to be established between the corresponding product(s) in the database. Same or similar products are defined in VICH GL24 on pharmacovigilance of veterinary medicinal products: management of adverse event reports (AERs)). This recommendation builds on current requirements in Volume 9B for marketing authorisation holders to provide this information in periodic safety update reports (PSURs) and the current process in place for the surveillance of centrally authorised veterinary medicinal products.

1.1.3. Use of standard terminology for coding adverse events

Recommendation

The information in the adverse event report shall be recorded and coded in the Union pharmacovigilance database using internationally agreed standard terminology adopted by EU institutions. The latest version of the standard terminology shall be used in line with the specified implementation dates.

Rationale

This recommendation builds on the experience gained with the application of Volume 9B, which states: "The use of controlled terminology is a crucial factor in harmonising the exchange of pharmacovigilance information" and this principle remains applicable for the future. Most standard terminology lists are published as guidelines in their own right. Implementation dates usually ensure sufficient 'lead-time' for stakeholders to prepare. Ensuring that the latest agreed version of standard lists for coding adverse events (e.g. Veterinary Dictionary for Drug Regulatory Activities (VeDDRA), species and breed list, VICH GL42 data elements guideline) are used will improve consistency of adverse event data. This will facilitate analysis of adverse event data and ultimately enhance the quality of evaluation within the signal management process.

Duplicate detection algorithms use fields containing standard terminology. Therefore, the above recommendation also serves to minimise the risk of duplicate adverse event reports and the administrative burden associated with their subsequent management. With the new reporting time-frame and routes defined in Regulation (EU) 2019/6 (i.e. the 30-day time-frame for reporting of adverse events and direct reporting from marketing authorisation holders and competent authorities into the Union pharmacovigilance database) there is a risk for an increase in the number of duplicate reports in the Union pharmacovigilance database. Previously all EU adverse events were reported via the national competent authorities which often performed essential duplicate control of adverse event reports before transmission to EudraVigilance Veterinary and this will no longer take place with the direct submission to the database. This recommendation aims to ensure consistency of adverse event data and uphold the overall standard of quality of the data within the Union pharmacovigilance database.

1.1.4. Measures for ensuring data completeness

Recommendation

Marketing authorisation holders shall make reasonable efforts to request further information, as necessary, to enable investigation of adverse events, including the results of appropriate diagnostic tests to ensure that adverse event data reported to the Union pharmacovigilance database are complete.

Rationale

Comprehensive and good quality adverse event data is one of the fundamental pillars to ensure robust pharmacovigilance surveillance and requires strengthening in legislation to ensure marketing authorisation holders prioritise this.

For the signal management process as outlined in Regulation (EU) 2019/6 and based on the new adverse event reporting routes, strengthening the need for complete and good quality data is essential. With marketing authorisation holders in future reporting adverse events directly to the Union pharmacovigilance database, a data quality check conducted by the competent authorities will no longer take place prior to their evaluation. The quality check undertaken by competent authorities has proved to be a key factor in improving the quality of adverse event reports and ensuring compliance with the guidance in place for the current system. It is therefore crucial that marketing authorisation holders, as well as competent authorities, benefit from good quality data standards in adverse event reports as this is the basis for signal detection and a robust evaluation of the product. Therefore, the above recommendations are crucial to strengthen completeness of the adverse event data reported to the Union pharmacovigilance database within the specified time-frame which will ultimately lead to more comprehensive and reliable pharmacovigilance surveillance.

1.1.5. Requirement for English language summaries of adverse event reports (case narratives) reported in languages other than English

Recommendation

Where the case narratives and textual descriptions of adverse events are reported in any other official language of the Union than English, the marketing authorisation holder shall provide the original verbatim text and a summary thereof in English.

Member States may report case narratives in their official language(s). For those reports, case translations in English shall be provided where requested by the Agency or other Member States for the evaluation of potential signals.

English shall be used for the reporting of adverse events originating outside the Union.

Rationale

Experience to date emphasises the need to ensure English translations of case narratives of adverse events that were reported in different languages in order to ensure effective surveillance. This is already in practice for human pharmacovigilance (see Commission Implementing Regulation (EU) No 520/2012 Article 28(4)) and to a certain extent in veterinary pharmacovigilance. In general, it is understood that most qualified persons for pharmacovigilance in multi-national companies would use English translations of adverse events for continuous surveillance of their veterinary medicinal products. The requirement for translation of case narratives into English is also consistent with the approach agreed at VICH (VICH Electronic Standards Implementation Expert Working Group (ESI EWG) Concept paper on revisions of VICH pharmacovigilance guidelines (VICH GL24, VICH GL29)).

The majority of structured fields can automatically be displayed in the English language in the Union pharmacovigilance database as such fields utilise drop-down-lists or a certain standardised reporting format (e.g. for dates).

1.1.6. Requirements for reporting adverse events published in scientific literature

Recommendation

Marketing authorisation holders shall monitor the scientific literature to identify any adverse events concerning their product(s) regularly.

The methodology for monitoring literature shall be described in guidance published by the Agency. The methodology for monitoring literature shall be undertaken in accordance with a risk-based approach, taking into account, at least, but not limited to, the following: type of product, length of time on the market and stability of the pharmacovigilance profile.

Pursuant to Article 76(2) the literature references for adverse events identified in publications shall be recorded in the Union pharmacovigilance database. Additional relevant identifiers including at least a digital object identifier, standardised[2], should also be recorded.

Rationale

According to Article 77(4) the marketing authorisation holder '… shall continuously evaluate by appropriate means the benefit-risk balance of this veterinary medicinal product….'. It is therefore considered essential that marketing authorisation holders are aware of current research and are up to date with the latest findings. This can only be guaranteed if literature searches are conducted on a regular basis, taking into account a risk-based approach to ensure this action is proportionate. Marketing authorisation holders already routinely monitor scientific literature to keep up to date with the latest scientific developments and with the use of their product. Therefore, this recommendation does not constitute an additional burden for pharmacovigilance. Any pharmacovigilance information arising from this ongoing activity shall be evaluated and submitted accordingly to the Union pharmacovigilance database.

Experience gained with the reporting of scientific literature in PSURs shows that more detailed guidance will be needed, addressing the level of detail of searches to be conducted, the type and number of search terms applied, and number of searches performed. These parameters may vary significantly, for example, with the choice of literature databases searched.

1.1.7. Reporting of adverse events following the use of human medicinal products

Recommendation

Adverse events in animals following the use of human medicinal products should be reported to the competent authorities responsible for veterinary medicinal products. In order to encourage reporting of adverse events in animals following the use of human medicinal products pursuant to Article 73(2), competent authorities should pro-actively communicate to veterinarians and other healthcare professionals on adverse events in animals following the use of human medicinal products that were reported to them.

Rationale

Monitoring adverse events following the use of human medicinal products in animals is now within the scope of veterinary pharmacovigilance. This practice [in accordance with the current 'prescribing

[2] DOI = digital object identifier, standardised
- (ISO 26324, Information and Documentation — Digital Object Identifier System (2012),
- Mechanism for, and emphasis on, enabling re-use of other existing identifier schemes, e.g., ISBN; see "DOI System and Standard Identifier Schemes".)

cascade', and as set out in Articles 112, 113 and 114 of Regulation (EU) 2019/6] is however well-established within veterinary medicine. Pharmacovigilance information on the use of human medicinal products in animals is important for veterinarians to improve their knowledge on the safe use of human medicinal products. However, marketing authorisation holders for human medicinal products do not have pharmacovigilance reporting requirements for adverse events reports in animals, and it cannot be expected that they take regulatory action on the basis of the use of their products in animals. Therefore, there is a risk that adverse events reported to human marketing authorisation holders may be 'lost' and not be incorporated in the veterinary pharmacovigilance system, and it is necessary to clarify the routes for reporting of such adverse events in legislation. To ensure that these events are captured within the veterinary pharmacovigilance system, veterinarians and other health-care professionals should be encouraged to report such adverse events to competent authorities responsible for veterinary medicinal products. It is foreseen that, where necessary, competent authorities will communicate issues relating to use of human medicinal products in animals to veterinarians and other product users e.g. via publications in veterinary journals and direct health-care professional communication. This information could also potentially contribute to improving availability of medicinal products as it provides empirical evidence on the use of products under field conditions.

1.2. Provision of data for calculation of incidence of adverse events reported to the pharmacovigilance database

Recommendation

Marketing authorisation holders shall provide the total estimated number of animals treated in the European Union for each of their veterinary medicinal products and for each target species, presented by pharmaceutical form and strength.

Marketing authorisation holders shall provide the estimated number of animals treated in third countries for each of their veterinary medicinal products and for each target species, presented by pharmaceutical form and strength.

Marketing authorisation holders shall record the methodology used for estimating the number of treated animals in the Union pharmacovigilance database.

This data shall be submitted annually to the Union pharmacovigilance database, in accordance with the established data lock point used for reporting the outcome of the marketing authorisation holders signal management process in line with Article 81 of Regulation (EU) 2019/6.

Rationale

Regulation (EU) 2019/6 requires the incidence of adverse events reported each year, broken down by veterinary medicinal product, animal species and type of adverse event to be published for the general public. According to Article 58(12) the annual volume of sales shall be recorded in the Union product database by the marketing authorisation holder for each of its veterinary medicinal products which provides a method for checking the reported incidence when required. The above recommendation builds on the current guidance in relation to PSURs currently given in Volume 9B on the provision of sales data and estimations of numbers of animals treated. Since pharmacovigilance reporting requirements also apply to adverse events from third countries, to enable comprehensive pharmacovigilance surveillance and evaluation of the worldwide pharmacovigilance experience of veterinary medicinal products, it is also necessary to ensure that the estimated number of animals treated worldwide is provided.

Incidence figures foreseen for publication will relate to adverse events for which a causal relationship between product use and the observed event may not yet have been established. Therefore,

disclaimers will be published to clarify the limitations of the data published and to highlight that no definitive conclusion on the causal association can be made on the basis of those figures alone.

Visibility of the methodology for calculation of the estimated number of animals treated used by marketing authorisation holders is required, and it should be recorded in the Union pharmacovigilance database. Without knowledge of the methodology applied by marketing authorisation holders it will not be possible for competent authorities and the Agency to understand the estimated number of treated animals and ascertain whether or not the agreed standards were applied (such as using the highest recommended dose as a worst-case scenario, average weight of the animals, etc.).

1.3. The signal management process defined in Article 4, provided for in Article 81 and explained in Recital 63 of the Regulation

Overview of the envisaged signal management process and risk-based approach, and rationale for the recommendations

The signal management process will enable continuous monitoring of the benefit-risk balance of a veterinary medicinal product and, if necessary, appropriate measures to be taken in line with Article 77(4). It is a core element of the pharmacovigilance system under Regulation (EU) 2019/6. It is therefore considered useful to first outline the entire process and provide the rationale for the recommendations on good pharmacovigilance practice, also highlighting where further guidance is envisaged to ensure an agile pharmacovigilance system that can be adapted based on experience gained.

Experience from signal management for human medicinal products and for centrally authorised veterinary medicinal products has demonstrated that, despite the availability of more powerful analytic tools and access to data over the life-cycle of a product, the process still requires expert resource and manual input, including clinical judgement, to assess the data constituting a signal. This may involve evaluation at the level of individual adverse event reports. Signal management can therefore not be considered an automated process. It should be acknowledged that observational data, such as pharmacovigilance data, frequently generate false positive signals. The key objectives of the new legislation include a reduction of administrative burden and making effective use of resources available within the veterinary pharmaceutical industry and the regulatory network in the EU. A risk-based approach, together with integrated Union pharmacovigilance and product databases, and clear and simple processes provide the best possible tools to achieve these objectives. Successful implementation of the requirements for signal management and application of a risk-based methodology necessitate further guidance, to be developed by the Agency. The elaboration of comprehensive guidance on the implementation of good veterinary pharmacovigilance practice, based on the recommended elements for legislation, will ensure the necessary flexibility to adapt the methodology to future needs as experience is gained with implementation of the new requirements from January 2022 onwards.

The proposed signal management process is described as follows:

- the marketing authorisation holder becomes aware of an adverse event directly when it is reported to them, or when it is identified through monitoring of scientific literature, or indirectly when their veterinary medicinal product(s) is/are cited in an adverse event report submitted to the Union pharmacovigilance database by other marketing authorisation holders or competent authorities.
- as a general principle, direct action on the basis of individual adverse event reports would only exceptionally be required. However, it may be the case that certain individual adverse event reports require in-depth analysis to assess the potential impact on the benefit-risk balance of a

product. It is intended to develop guidance on the type and nature of reports that may signal a change to the benefit-risk balance of a product or a new risk, requiring in-depth evaluation. This guidance will describe the risk-based approach in detail, based on the nature of the event, type of product, species affected and other factors. It will focus on identifying the scenarios that require notification to the competent authorities or the Agency within 30 days, in line with Article 81(2), and taking necessary action in accordance with Article 77(10).

- analytical tools will be available in the Union pharmacovigilance database for situations when a more in-depth analysis is considered necessary, or, as required, during the signal management process. Analytical tools will enable relative comparisons to be made between different products or product groups in the Union pharmacovigilance database, including analysis at active-substance level and stratified analyses focused on, for example, certain species or age groups. The best practice for identifying, validating and evaluating signals will also be outlined in the guidance. Marketing authorisation holders may also use additional data and analytical tools available to them for this purpose. Where marketing authorisation holders identify a change to the benefit-risk balance or a new risk, they shall notify the competent authorities or the Agency, as applicable, without delay and no later than 30 days, and take the necessary action in accordance with Article 77(10). The type of information concerning the marketing authorisation holders' signal management analysis that shall be recorded in the Union pharmacovigilance database will be outlined in the guidance referred to.
- for routine analyses, where marketing authorisation holders conclude there is no change to the benefit-risk balance of their products or no new risks are identified, no further action will be required. However, for certain types of adverse events (e.g. particular adverse events involving 'medically important VeDDRA terms' such as blindness, birth defects, etc.) marketing authorisation holders may be required to record a summary and conclusion of their analysis in the Union pharmacovigilance database, even when no regulatory action is considered necessary; this will be further outlined in the guidance to be developed. Such requirements are considered within the scope of Article 81 for recording the results and the outcomes of the signal management process in the Union pharmacovigilance database. Irrespective, and on a yearly basis, marketing authorisation holders shall confirm in the Union pharmacovigilance database that the signal management process has been conducted in line with the guidance published by the Agency and that the benefit-risk balance continues to remain favourable.

In practice, it is anticipated that certain types of products, for example, novel products, would require more frequent monitoring, whereas 'older' products, with an established and stable pharmacovigilance profile, would be monitored less frequently. For these older, established products, it is anticipated that marketing authorisation holders' pharmacovigilance activities would be limited to collecting and reporting of adverse events and that the depth and extent of analysis required in the signal management process could be minimal, reflecting a low level of risk. However, for all products and at least on a yearly basis, marketing authorisation holders are required to record in the Union pharmacovigilance database, a conclusion on the benefit-risk balance and confirm compliance with continuous monitoring of the benefit-risk balance as required in accordance with Article 77(4). Article 81 also stipulates that reference to relevant scientific literature shall be recorded in the Union pharmacovigilance database.

In accordance with Article 79(1), competent authorities and the Agency shall establish procedures for evaluating the results and outcomes of the marketing authorisation holders' signal management processes that are recorded in the Union pharmacovigilance database. To prioritise evaluation of signals relevant for safeguarding animal and public health and the environment, a risk-based approach will be outlined in guidance. Considering the resources available within the EU regulatory network and

to ensure efficiency while avoiding duplication of efforts, a work-sharing process for evaluation at Union level shall be established. It is proposed that the work-sharing is conducted on the basis of active-substance-grouping of veterinary medicinal products. The methodology, outlining the roles and responsibilities of competent authorities and the Agency, is proposed to be described in guidance and will include, in particular the potential for delegation of tasks to a competent authority in another Member State in line with Article 80.

Article 81(3) foresees the possibility of an *ad-hoc* targeted signal management process that may be triggered by a competent authority or the Agency in the interests of animal and public health and the environment. The competent authorities and the Agency may decide to perform such targeted signal management based on the evaluation of the outcome of the marketing authorisation holder's signal management process. However, such targeted signal management may also be considered necessary on the basis of any information received by competent authorities or the Agency.

1.3.1. Definition of a signal

Recommendation

A signal is information that arises from one or multiple sources (including observations and experiments) which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related adverse events, that is judged to be of sufficient likelihood to justify verificatory action.

1.3.2. Signal management activities undertaken by marketing authorisation holders

Recommendation

Marketing authorisation holders shall continuously monitor the benefit-risk balance of their products on the basis of information received from veterinarians and other healthcare professionals, the general public, or from adverse event reports submitted to the Union Pharmacovigilance database by other marketing authorisation holders or competent authorities, or from scientific literature.

Marketing authorisation holders shall use the Union pharmacovigilance database as part of their signal management process and monitor the data available in the Union pharmacovigilance database with a frequency proportionate to the identified risks, the potential risks and the need for additional information. Marketing authorisation holders shall follow the methodology described in guidance published by the Agency.

When marketing authorisation holders identify a new risk or a change to the benefit-risk balance, a summary and conclusion of their analysis shall be recorded in the Union pharmacovigilance database when notifying the competent authority or the Agency, as applicable.

For analysis of particular signals, including those involving 'medically important VeDDRA terms', the competent authorities or the Agency may require marketing authorisation holders to record a summary and conclusion, even when the outcome is that there is no new risk or no change to the benefit-risk balance.

At least annually, marketing authorisation holders shall record in the Union pharmacovigilance database a conclusion on the benefit-risk balance of the product and confirm that the signal management process has been conducted in line with relevant guidance published by the Agency.

Where a marketing authorisation holder is responsible for a same or similar veterinary medicinal product authorised in different Member States through different authorisation procedures, the signal

management process should be performed for all the products combined and recorded accordingly in the Union pharmacovigilance database.

Rationale

See the detailed explanation in section 'Overview on the signal management process and risk-based approach and rationale for recommendations' above under point 1.3 for the overall rationale. The rationale supporting the recommendation for the establishment of a list of 'medically important VeDDRA terms' is however detailed here. To facilitate signal prioritisation, it is proposed that a list of 'medically important VeDDRA terms' is established and used. This is based on the analogous 'medically important event' used in human pharmacovigilance to describe serious events that may not be immediately life-threatening or result in death or hospitalisation, but which might jeopardise the patient or might require intervention. A list of important medical events (IME) was developed, based on the Medical Dictionary for Regulatory Activities (MedDRA). The IME list facilitates the classification of adverse events as well as aggregated data analysis and case assessment in the frame of the day-to-day pharmacovigilance activities. A similar list for use in the signal management process in veterinary pharmacovigilance is proposed, taking into account species specificities e.g. recumbency in large animals, injection site sarcomas in cats. It is proposed that the list of 'medically important VeDDRA terms' is established by the Agency, since VeDDRA is owned by the CVMP. Having the list established as a CVMP guideline would also facilitate the expected regular updates required. The list of 'medically important VeDDRA terms' should be developed on the basis of the current list in the CVMP questions and answers document on serious non-fatal adverse events and reporting rules (EMA/CVMP/PhVWP/303762/2012-Rev.1).

1.3.3. Signal management related activities undertaken by competent authorities and the Agency

Recommendation

Competent authorities and the Agency shall establish procedures and guidance for signal management to be undertaken by marketing authorisation holders for continuous evaluation of the benefit-risk balance of their veterinary medicinal products. The guidance and methodology shall follow a risk-based approach, enabling marketing authorisation holders to prioritise and to determine the depth and extent of evaluation required. The methodology shall outline the steps in the signal management process and analytical tools available to evaluate data in the Union pharmacovigilance database. The risk-based approach shall take into account, but not be limited to, the following: type of product, length of time on the market, stability of the pharmacovigilance profile of the product(s) or the active substance(s) and the relative severity of the adverse events reported.

The Agency shall establish and maintain a 'list of medically important VeDDRA terms', to be used by marketing authorisation holders, competent authorities and the Agency to facilitate prioritisation.

The Agency shall support the monitoring of the safety of veterinary medicinal products by means of the Union pharmacovigilance database by providing access for competent authorities and marketing authorisation holders to the following:

a) database tools for reviewing adverse events in the Union pharmacovigilance database in relation to an active substance or a medicinal product; and

b) statistical signal detection methods.

Competent authorities and the Agency shall follow a risk-based approach, in line with the guidance published by the Agency, for evaluating the results and outcomes of marketing authorisation holders'

signal management processes as well as for the adverse events reported to competent authorities in accordance with Article 79(1) of Regulation (EU) 2019/6.

The risk-based approach for evaluating the results and outcomes shall take into account, but not be limited to, the type of product, length of time on the market, stability of the pharmacovigilance profile of the product(s) or the active substance(s) and the relative severity of the adverse events reported in animals and humans.

In accordance with Article 79(1) the competent authorities and the Agency shall establish procedures to evaluate the results and outcomes of the signal management process recorded by marketing authorisation holders in the pharmacovigilance database. To this end, the competent authorities and the Agency will develop guidance for the active-substance based work-sharing procedure to be followed, including the roles and responsibilities for competent authorities and the Agency, criteria for allocation and grouping products and the methodology to be applied for evaluation of the signal management outcomes recorded by marketing authorisation holders.

The competent authorities and the Agency may decide to perform targeted signal management processes on the basis of the evaluation of the outcome of the marketing authorisation holder's signal management processes. A targeted signal management process may also be considered necessary on the basis of any information or request received.

The competent authorities and the Agency shall record the outcome of the evaluation of their signal management processes, including the targeted signal management processes, and any recommendations for regulatory action in the Union pharmacovigilance database, for consideration by the Committee for Veterinary Medicinal Products (CVMP) Pharmacovigilance Working Party (PhVWP-V). The CMDv and the CVMP shall examine advice from the PhVWP-V, and, where necessary, recommend actions and risk management measures to the competent authorities and the Commission, as applicable.

Rationale

See the detailed explanation in section 'Overview of the signal management process and risk-based approach and rationale for recommendations' above under point 1.3 for the overall rationale. The rationale for the requirement for the competent authorities and the Agency to use the Union pharmacovigilance database to record the outcome of their evaluation of the marketing authorisation holders signal management process is outlined here. While not laid down explicitly by the provisions of Regulation (EU) 2019/6, the recommendation is proposed for consistency to ensure that competent authorities and the Agency also record the outcomes of their evaluation in the Union pharmacovigilance database since marketing authorisation holders are also required to record the outcome of the signal management process in the same database. This will ensure that the Union pharmacovigilance database is the single reference point for pharmacovigilance information in the EU. And this will enable information to be easily shared and accessible throughout the EU regulatory network, facilitate cooperation and management for the regulatory work-sharing, and minimise administrative burden by ensuring the information is available at a single point within the network which would avoid, for example, the need to create and manage documents stored outside the database and therefore not be readily accessible to the regulatory network.

1.3.4. Alerts related to pharmacovigilance data

Recommendation

The data-processing network of the Union pharmacovigilance database as described in Article 74(5) of Regulation (EU) 2019/6 shall be used by Member States, the Commission, the Agency and marketing authorisation holders for communication and evaluation of alerts related to pharmacovigilance data.

Rationale

Article 74(5) of Regulation (EU) 2019/6 states that the system of the pharmacovigilance database shall be established as a data-processing network allowing transmission of data between Member States, the Commission, the Agency and the marketing authorisation holders to ensure that in the event of an alert related to pharmacovigilance data, options for risk management and any appropriate measures can be considered as referred to in Articles 129, 130 and 134.

To enable efficient and timely communication on alerts related to pharmacovigilance data (which may include potential serious risks to human or animal health or to the environment (as defined in Article 4(42)) and the processing of the signal management outcomes, it is essential that the data-processing network is used by all marketing authorisation holders, competent authorities and the Agency. This will ensure a comprehensive and streamlined approach, optimising the potential of the Union pharmacovigilance database by enabling all veterinary pharmacovigilance data to be integrated within a single system.

Currently the veterinary pharmacovigilance rapid alert system in place for rapid communication within the regulatory network is based on the circulation of word documents via Eudranet. It is not integrated with the current electronic reporting and data analysis systems used in veterinary pharmacovigilance, i.e. EudraVigilance Veterinary and the data warehouse. Using the Union pharmacovigilance database for communication and evaluation of pharmacovigilance alerts would ensure a comprehensive and streamlined approach to pharmacovigilance surveillance without having to access data from disparate sources. In human pharmacovigilance, rapid alert communication operates within the respective pharmacovigilance database, which has been found an efficient system.

Furthermore, the current pharmacovigilance rapid alert system does not include marketing authorisation holders. Using the Union pharmacovigilance database for communicating alerts would have the advantage of involving marketing authorisation holders and improve the efficiency and effectiveness, as alerts may require prompt consideration and potential action.

2. Pharmacovigilance communication

2.1. Communication plan and communication procedures requirements

Recommendation

The marketing authorisation holder is required to have a communication plan. This plan shall identify the relevant stakeholders in the EU (including customers) and outline the approach(es) to communicate with them in a timely manner, in cases of urgent safety concerns arising from pharmacovigilance data, any urgent regulatory actions, or in relation to other relevant pharmacovigilance information.

The communication plan is an integral part of the marketing authorisation holder's pharmacovigilance system.

The communication plan shall include, as a minimum, information (approaches, processes and/or procedures) that will enable:

- identification of the target audience;
- identification of an effective means for communicating with the intended target audience;
- identification of specific objectives of the communication (e.g. notification of a change in the conditions of use of a product to mitigate an identified risk);
- ensuring the relevance and clarity of the information for the intended target audience;
- identification and coordination of stakeholders involved in the communication; and
- measuring the effectiveness of the communication.

In relation to findings identified by the marketing authorisation holder, the relevant competent authority or the Agency that may require urgent regulatory action and communication to relevant stakeholders, and where the marketing authorisation holder intends to communicate in line with Article 77(11), the text should be formulated in line with the relevant guidance, published by the Agency.

The Agency shall establish procedures for adequate, prompt and coordinated communication by marketing authorisation holders, competent authorities and the Agency, in case of concerns arising from pharmacovigilance data or other information impacting animal or public health or the environment.

Rationale

There have been several examples where it was important to reach certain groups of stakeholders in relation to new insights following the analysis of pharmacovigilance information or in relation to regulatory actions. Experience has shown that preparedness is important to enable communication, in particular in case of urgency. The recommendations aim at ensuring that the marketing authorisation holder is prepared for any communication with respect to findings warranting potential urgent regulatory action, or for informing stakeholders about specific pharmacovigilance findings. The format and content of the communication plan will be described in guidance published by the Agency. Experience has also shown that it is important to establish guidance on communication that will ensure a balanced, non-selective and neutral representation of the facts and coherent communication by the different parties. It is acknowledged that additional guidance may be applicable in certain Member States, to address specific national situations or legislative requirements.

Similar to the obligation for marketing authorisation holders, regulatory authorities should also be required to have the necessary procedures in place to initiate and manage urgent communication, as required. There is already practical but limited experience with the incident management plan for medicines for veterinary use (EMA/711053/2010 Rev.2) that enables regulatory authorities to exchange information and coordinate regulatory action in case of incidents or crises. Coordinated communication is an important aspect for which preparedness is key for all stakeholders including regulatory authorities and the Agency. The recommendations aim at ensuring that procedures will be put in place that ensure adequate communication.

2.2. Availability of a link to the electronic version of the latest summary of product characteristics in the printed package inserts

Recommendation

The marketing authorisation holder shall ensure that a link to the latest updated electronic version of the full text of the summary of product characteristics (SPC) is available on the printed version of the package insert.

Rationale

At present, when regulatory action is taken that, for example, involves changes to the product information, a product already on the market will have an outdated printed package insert until the newly printed package inserts reach the market. This recommendation recognises the ability to enable easy access to relevant electronic information through the use of, e.g., QR codes. Compared to information on printed package inserts, certain information reachable through a QR code on, e.g., a smart phone can be presented in a more readable format and would also allow access to show safe use instruction graphics, instruction movies etc. The aim is to ensure a link to the latest SPC information that is publicly and electronically available from the Union Product database on the printed package leaflet. Guidance is foreseen to be developed to outline best practice which will evolve, taking into account the ever changing electronic "media" developments. The guidance may also outline time limits for "outdated" information to remain on the market.

3. Pharmacovigilance inspections

3.1. Definition and subject of pharmacovigilance inspections and controls

Recommendation

Control as defined in Article 4(32) of Regulation (EU) 2019/6, includes pharmacovigilance inspections which may be performed as on-site or remote inspections.

Subject to pharmacovigilance inspections are holders of a marketing authorisation for a veterinary medicinal product, the respective representative responsible for the reporting of adverse events according to Article 14(1)(a) and (l) and Article 77(3) of Regulation (EU) 2019/6, and any party carrying out pharmacovigilance activities in whole or in part, on behalf of, or in conjunction with the holder of the marketing authorisation for the veterinary medicinal product, thereafter referred to as the "inspected party".

Rationale

The definition of control in Regulation (EU) 2019/6 does not specify the possibility for inspections to be carried out on-site or remotely. It is however important to clarify that controls include pharmacovigilance inspections, irrespectively if they are conducted on-site or remotely (off-site) to ensure there is clear legal basis for the conduct of those inspections in accordance with Article 123(6) of Regulation (EU) 2019/6.

Article 77 of Regulation (EU) 2019/6 states that "Where the pharmacovigilance tasks have been contracted out by the marketing authorisation holder to a third party, those arrangements shall be set out in detail in the pharmacovigilance system master file." It is essential to clarify that any third party carrying out pharmacovigilance activities in whole or in part, on behalf of, or in conjunction with the marketing authorisation of the veterinary medicinal product may be subject to pharmacovigilance inspections as otherwise competent authorities may not be able to verify compliance of the

pharmacovigilance system with the Regulation. This provision will also ensure that contracts between entities include clear roles and responsibilities regarding pharmacovigilance activities and safety exchange agreements are in place, as appropriate. In the recommendations the term "inspected party" is used to refer to any party that can be subject to inspections to verify compliance with the provisions of Regulation (EU) 2019/6. Competent authorities may use on-site or remote inspections and documentation review for the verification of compliance with the Regulation. Further guidance should be developed to clarify the parties to be inspected and to describe further remote inspections.

3.2. Objectives of pharmacovigilance inspections

Recommendation

Competent authorities shall carry out pharmacovigilance inspections with the following objectives:

- to inspect the pharmacovigilance system in place and the corresponding pharmacovigilance system master file and verify compliance with Regulation (EU) 2019/6, the implementing act and good pharmacovigilance guidance;
- to determine that the inspected party has personnel, systems and facilities in place to meet their pharmacovigilance obligations and that they are inspection-ready;
- to determine that contractual arrangements are in place including the clear description of the roles and responsibilities for the pharmacovigilance activities subcontracted and provisions for inspection and audit;
- to identify, record and address non-compliance with the legislation or relevant guidelines;
- to follow up the implementation of corrective and prevention action plan of the inspected party;
- to use the inspection results as a basis for enforcement action, where considered necessary.

Rationale

The high-level objectives of pharmacovigilance inspections need to be defined as the basis for inspection planning, inspection scope and inspection follow up. Third parties that form part of a pharmacovigilance system should be inspection-ready and should accept to be audited and inspected, as necessary, and this should be reflected in the relevant agreements. The recommendation aims at enforcing these principles.

Additional guidance will need to be developed to describe inspection follow up and enforcement activities by Member States for non-compliance with Regulation (EU) 2019/6, as non-compliance can result in damage to public and animal health and the environment.

3.3. Inspection types

Recommendation

Inspections shall be carried out by competent authorities on a regular basis at appropriate intervals as routine inspections, or as "targeted" inspections.

The frequency and scope of the inspections should be adjusted (reduced or increased) based on a risk-based approach.

The frequency and extent of all inspection types shall be appropriate to the potential risks associated with the respective veterinary medicinal products and the inspected party.

Inspections can be conducted announced or unannounced.

Inspections can be product-specific or general system inspections.

Rationale

Based on the criteria for the risk-based approach on controls described in Article 123(3) of Regulation (EU) 2019/6, inspections can be carried out routinely or as targeted inspections that may cover the overall pharmacovigilance system, part of it or specific products.

Targeted inspections are "for cause" inspections, which may be triggered for various reasons, such as non-compliance with reporting obligations, delays or failure to identify or communicate a change in the risk-benefit balance for one or more veterinary medicinal products. Complementary guidance will be developed on criteria to trigger targeted inspection.

3.4. Sites to be inspected

Recommendation

The sites to be inspected shall comprise the site where the pharmacovigilance system master file is located, and any other site of the inspected party required to confirm compliance with pharmacovigilance obligations in accordance with Regulation (EU) 2019/6. With regard to the latter, the site to be inspected may be located in the Union or outside the Union.

Rationale

The focus of pharmacovigilance inspection planning will be the sites conducting pharmacovigilance activities in the Union. It is recommended that there is clear provision to inspect sites or entities carrying out pharmacovigilance activities in whole or in part, on behalf of, or in conjunction with the marketing authorisation holder, inside and outside the Union when this is necessary to confirm the holder's compliance with pharmacovigilance obligations as set in the Regulation.

3.5. Inspection process

Recommendation

Pharmacovigilance inspections should be planned, coordinated, conducted, reported on and followed-up according to the processes described in the relevant guidelines, published by the Agency.

Rationale

In order to ensure that the Member States follow harmonised inspection practices it is important to foresee the development of guidelines that will describe the planning, coordination, conduct, reporting and follow-up of inspections.

3.6. Requirements for the marketing authorisation holder of veterinary medicinal products and parties performing pharmacovigilance activities on their behalf verified during pharmacovigilance inspection

3.6.1. Pharmacovigilance System

Recommendation

The pharmacovigilance system to be established by the marketing authorisation holder, pursuant to Article 77(1) of Regulation 2019/9, shall comprise at the minimum:

1. a qualified person responsible for pharmacovigilance and a back-up procedure in case of absence;

2. a clear organisation structure of the different units of the pharmacovigilance department and the attribution to / position in the company;
3. sufficient and adequately trained personnel;
4. a system of data handling and recording for collecting, collating and evaluating information on the adverse events in EU or in a third country and that there is a process to ensure the quality of data in the reports sent to the union pharmacovigilance database. [in accordance with guidance, to be published by the Agency;
5. a validated database or any other appropriate recording system for the management of adverse event data and pharmacovigilance related data;
6. a system for continuous monitoring of the risk-benefit balance of the veterinary medicinal product(s) via the signal management process including signal detection and analysis, procedures for managing the result of this monitoring and for the decision-making process in order to ensure that appropriate measures are taken;
7. the operation of a risk management system, including monitoring of the outcome of risk minimisation measures and implementation of a risk communication plan comprising procedures for communicating safety concerns to the Agency, to competent authorities, to healthcare professionals and to the general public;
8. archiving arrangements that ensure the safety and the timely availability of pharmacovigilance data and other relevant data for the pharmacovigilance system;
9. contractual arrangements with all other parties involved in pharmacovigilance processes, including the relevant safety data exchange agreements and arrangements for ensuring that the marketing authorisation holder of the veterinary medicinal product can audit the respective parties regarding pharmacovigilance activities;
10. a quality management system including procedures in place, documented in writing, for the pharmacovigilance activities and the respective audits.

Rationale

Regulation (EU) 2019/6 does not include specific reference to quality management systems as a requirement. It is however considered necessary to define the minimum requirements for an adequate pharmacovigilance system. These will be the elements included in a full system pharmacovigilance inspection scope. Having a quality management system for the performance of pharmacovigilance activities is considered crucial for the performance and compliance of the pharmacovigilance systems in place. Therefore, it is recommended that emphasis is given to the quality management system as a requirement, and the definition of what are considered minimum requirements for an adequate quality management system, similarly to what is foreseen in the implementing regulation for human pharmacovigilance (Regulation (EU) 520/2012 chapter III).

Further details on requirements for the quality management system should be given in relevant guidelines to be developed. There is comprehensive guidance available related to human medicinal products however it needs to be further discussed which elements are fit-for-purpose minimum quality system requirements for veterinary pharmacovigilance systems.

3.6.2. Qualified Person responsible for pharmacovigilance (QPPV)

Recommendation

By means of inspections it shall be demonstrated that the qualified person responsible for pharmacovigilance is appropriately qualified, with documented experience in pharmacovigilance in order to fulfil the responsibilities and tasks of the position in accordance with Article 78 of the Regulation (EU) 2019/6, and that, when necessary, appropriate measures are put in place to ensure that the work of the qualified person responsible for pharmacovigilance is not influenced by the activities of the sales or distribution units.

Where the qualified person has not completed training as a veterinary surgeon in accordance with Article 38 of Directive 2005/36/EC of the European Parliament and of the Council of 7 September 2005 on the recognition of professional qualifications, it shall be ensured that the qualified person responsible for pharmacovigilance is assisted by a person trained as a veterinary surgeon. This arrangement shall be duly documented.

Back up procedures to ensure business continuity with regard to the fulfilment of pharmacovigilance obligations shall be established.

The marketing authorisation holder shall ensure that the qualified person responsible for pharmacovigilance has sufficient authority over the pharmacovigilance system in order to promote, maintain and improve compliance with pharmacovigilance tasks and responsibilities listed in the Article78 of the Regulation (EU) 2019/6.

Rationale

It is recommended that emphasis is given to training and qualification of the qualified person responsible for pharmacovigilance and pharmacovigilance staff in relation to their roles and responsibilities. They should be trained in pharmacovigilance processes and requirements in such way that they are able to comprehend the different aspects of a pharmacovigilance system. It is important that if the qualified person has not completed training as a veterinary surgeon, s/he is assisted by a veterinary surgeon. Similar provision is foreseen in the implementing regulation for human pharmacovigilance (Commission Implementing Regulation (EU) 520/2012, Chapter III, Article 10).

Where conflicts exist which may impact on the activities of the qualified person responsible for pharmacovigilance, measures, such as a procedure for identifying and addressing potential conflicts, and decisions taken (e.g. delegation and increasing of resources), should be in place and described in the pharmacovigilance system master file, when this is applicable. This will help to ensure that the qualified person responsible for pharmacovigilance is free from influence from commercial operations, enabling them to perform their duties appropriately.

3.7. Requirements for the Agency and the competent authorities in the Member States in relation to pharmacovigilance inspections

3.7.1. Conduct of inspection

Recommendation

Further to Article 126(4) of Regulation (EU) 2019/6, the competent authority of the Member State in which the pharmacovigilance system master file is located is designated as the supervisory authority for the corresponding pharmacovigilance system and shall carry out inspections of the pharmacovigilance system and the pharmacovigilance system master file.

In line with Article 126(5) and pursuant to Article 80 of Regulation (EU) 2019/6, the role of a supervisory authority may be delegated to other Member States. At national level, the competent authority shall have the right to inspect any party, as necessary, to confirm compliance with pharmacovigilance obligations in accordance with Regulation (EU) 2019/6.

The Agency in collaboration with Member States, shall develop guidance establishing the procedures to be followed in order to ensure the regularity of inspections without unnecessary repetition.

Rationale

To ensure the regularity of inspections without unnecessary repetition it is recommended to introduce the concept of supervisory authority which by default will be the competent authority of the Member State in which the pharmacovigilance system master file is located.

The supervisory authority will be responsible for the controls and inspection of the pharmacovigilance system(s) with pharmacovigilance system master file(s) located in their territory unless they delegate this activity to a competent authority in another Member State via written agreement, in accordance with Article 80 of the Regulation.

3.7.2. Sharing of information and inspection programme

Recommendation

The Agency and the competent authorities shall cooperate to facilitate the exchange of information on inspections and in particular:

1. information on inspections planned and conducted in order to avoid unnecessary repetition and duplication of activities and optimising inspection resources;
2. information on the outcome of pharmacovigilance inspections in accordance with Article 126(6) of the Regulation (EU) 2019/6 including corresponding corrective and preventive actions;

Pharmacovigilance inspection programmes should be established at Union and national levels, and will need to be adjusted, in a risk-based approach, at least yearly based on the criteria set out in Article 123(3) of Regulation (EU) 2019/6.

Rationale

It is recommended that the high level principle of sharing of information regarding planned and conducted inspections, inspection outcomes and follow up (including corrective and preventive measures) is an obligation for Member State competent authorities to avoid unnecessary repetition and duplication of activities in the Union and optimising inspection resources, to facilitate risk-based planning of controls, including inspections, delegation and cooperation among EU Member State inspectorates.

3.7.3. Qualification and training of inspectors

Recommendation

Any inspector or representative of a competent authority should be qualified and trained adequately. Details of the necessary qualification and training will be defined in relevant guidance, published by the Agency.

Rationale

It is recommended to include provisions for adequately qualified and trained inspectors to ensure this is taking the appropriate attention at Member State competent authority level.