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Reflection paper on non-spontaneous adverse event reports (peer-reviewed literature, internet and social media)

Draft

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1. Introduction

It is acknowledged that the topics of reports published in peer-reviewed worldwide literature and information on adverse events from the internet are introduced in Volume 9B of the Rules Governing Medicinal Products in the European Union (EU). However detailed guidance on handling such reports is not given and interpretation of requirements has been variable between national competent authorities (NCAs) to date.

It is noted that the discussion of pharmacovigilance issues is not limited to the formal pharmacovigilance system. On the contrary there is a wealth of structured and non-structured information in:

- the scientific literature;
- the internet in general (marketing authorisation holder (MAH) web sites, breeders associations etc.); and
- interest groups on social media etc.

This draft reflection paper aims to examine the current situation on obtaining pharmacovigilance information from non-spontaneous sources (peer-reviewed literature, internet and social media) as a basis for the development of future guidance. Non-spontaneous reports from studies (e.g. post-authorisation safety studies and clinical trials etc.) are excluded from the scope of this document. It is acknowledged that the scope of topics covered by this paper is broad and diverse, but this reflects the nature of pharmacovigilance reports from informal sources such as the internet.

2. Discussion

2.1 Peer-reviewed published literature

It is presently a requirement that MAHs should regularly perform a literature search as part of the periodic safety update report (PSUR). However, it is recommended that MAHs search the literature more regularly as part of their ongoing surveillance/signal detection procedures and at least yearly for products on a three-yearly PSUR reporting cycle. Unless there are serious problems that require urgent attention (e.g. contacting authors) such issues should not usually be reported as spontaneous adverse events and would be expected to be included in the next PSUR.

Limitations of the current guidance for searching the published literature are recognised and discussed as follows:

1. Volume 9B requires that the MAH is only requested to perform a product specific search. Due to the way that scientific articles are written, it is acknowledged that product names are rarely included as a key word or mentioned in the abstract. It is recommended to begin literature searches based on the active substance which should then be narrowed down to the individual product. Similarly the search terms for 'adverse events' should not be too restrictive and other terms should be used e.g. adverse reaction, side effect, toxicity. The MAH is expected to consider reports from other products than their own if the reaction of interest is related to the active substance and/or if the specific product cannot be identified. All reports that clearly relate only to competitor products would be excluded.
2. Volume 9B does not specify the database(s) which should be included in the search. The choice of databases should also be discussed. For example databases such as Medline may not necessarily

capture all national veterinary journals. There may also be problems with using Google Scholar which may not be representative of all relevant articles. It is preferable to ensure that a variety of databases and/or search engines are searched including CAB Abstracts, Google Scholar, Medline, PubMed, Scopus and Web of Knowledge, for example.

Relevant sources other than peer reviewed literature should be searched, where possible, for reports indicative of resistance to antimicrobials or antiparasitics e.g. national databases on minimum inhibitory concentration (MIC) values. Such databases are publically available in e.g. Denmark (Danmap), Norway (NORM-VET), Finland (FINRES), the Netherlands (MARAN) and Sweden (SVARM).

2.2 Reports derived from the internet

Non-spontaneous adverse event reports and pharmacovigilance information may originate from an ever increasing number of online resources. In some Member States, although there is not an agreed common practice as yet, some of the anecdotal issues indicative of adverse events that MAHs and NCAs become aware of are then further investigated to determine whether they fulfil the criteria for an adverse event in which case they are then reported and analysed as usual. The main sources of such information that NCAs are currently aware of are discussed below.

2.3 MAH hosted websites and social media accounts

Most MAHs have an active presence on the internet in the form of websites and social media accounts. It is acknowledged that this is primarily for commercial reasons and they do not always appear to promote pharmacovigilance reporting. However, many MAH hosted websites have 'contact us' forms. Experience gained on pharmacovigilance inspections indicates that this route is frequently used to report adverse events. Similarly MAHs should be encouraged to make use of social media to inform product users how and when to report adverse events. In any case all such potential adverse events identified via company websites or social media accounts should be followed up by MAHs, as is done for reports identified by any other means.

2.4 Groups of animal owners on the internet

Social networks open up the possibilities of discovering and learning new information, sharing ideas and interacting with others. There can also be formation of new alliances between people that share common interests. It is noted that interest groups on social media platforms have become a trusted source of new information for animal owners.

Various breed organisations and interest groups have *fora* on the internet often with discussion and chat rooms. For many animal owners their first reaction in the case of adverse events is to put a question on these *fora* either as a warning or seeking advice. Although this information may be important it may be complicated to use it for surveillance purposes for the following reasons:

- The groups may be numerous and very diverse. They are often loosely organised making it time-consuming to trawl through all of the information available from these sites;
- The reports of adverse events are not made in a systematic way. Information on product, time to onset of the event, etc. may be missing. It is not always clear when such adverse events may have occurred as there may often be reference to historical events. These factors make it difficult to identify individual adverse events which should be reported and whether the events relate to duplicate reports; and

- The events may go 'viral' in the sense that a given type of reaction will spur several responses and discussion threads. So some types of adverse events may be over-represented.

MAHs would not be expected to trawl the internet to search for potential adverse event reports. However if the MAH becomes aware of potential adverse events, every effort should be made to follow up on the reports to obtain at least the minimum reporting criteria so that the events can be channelled into the formal pharmacovigilance reporting system. In cases where the minimum criteria for a valid adverse event report have not been met after efforts to investigate the potential event, it is recommended that MAHs keep a record of these data.

2.5 Potential for making more use of social media and internet

Some of the areas where internet and social media could be exploited better are discussed below. MAHs may choose to make further use of the information on the internet and social media by capturing product and substance specific information by some of the following means:

- Following selected *fora* on the internet;
- Setting-up search profiles on e.g. Google or Facebook to capture recent discussions. Google offers the possibility of advanced searching to create a profile for example '(adverse event) AND (dog OR cat OR ….)' to capture a broad range of sites. It should be noted that even a regular search may not capture the most recent threads on the different *fora*.

MAHs are expected to review information from social media when made aware of a discussion of a potential safety problem and to decide whether the information requires further action. If MAHs have actively monitored social media for adverse events, they should be encouraged to state that in the PSURs.

3. Conclusion

It is encouraged and expected that MAHs follow the products they are responsible for on peer-reviewed literature and ensure a general awareness of pharmacovigilance information from informal sources including social media. It is expected that this follow-up is regular and that a proactive approach is taken to ensure potential adverse events are identified and evaluated.

4. References

Committee for Medicinal Products for Veterinary Use (2015). Reflection paper on promotion of pharmacovigilance reporting (EMA/CVMP/PhVWP/390033/2014) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500184528.pdf

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