EGGVP comments as regards the **EMA scientific recommendations** on delegated and implementing acts as part of the implementation of the new veterinary medicines Regulation 2019/6

Subject: **Good pharmacovigilance practice (Article 77 (6))**

Preamble

On 6 February 2019 the European Commission sent a request to the European Medicines Agency for scientific for scientific recommendations on good pharmacovigilance practices.

The Committee for Medicinal Products for Veterinary Use (CVMP) adopted the scientific recommendation which was sent to the European Commission on 29 May 2020.

On 12 June 2020, the European Commission (DG Sante) contacted EGGVP with a kind request for written comments as regards the EMA advice, in the context of a targeted stakeholder consultation.

EGGVP highly values this consultation and the opportunity to share its views on this topic, and thanks DG Sante for the initiative.

EGGVP general comments

IMPACT FOR INDUSTRY

The scientific recommendations set up by the CVMP provide the general principles and key recommendations that will be further developed by means of guidelines addressing the specific details required for a full and appropriate implementation. How effective the new pharmacovigilance provisions will be in supporting the reduction of administrative burden, both for regulators and industry (primary objective of the new veterinary legislation), will depend on outcome of these guidelines. However, some of the approaches made in the scientific recommendation entail a serious risk of regression away from this objective. It is the industry's concern that the goal may not be reached, even on the contrary. In particular provisions on reporting and recording of adverse events and the signal management process (see section 1 below) are much worrying in this regard, as the

workload seems to be considerably increased while bringing no visible improvements, in comparison to the current status quo, to the rest of the objectives of the new legislation: enhance of the internal market, increased availability of veterinary medicines and increased level of public health and animal health and environmental protection.

IMPLEMENTATION OF THE NEW RULES

In order to prevent the risks above mentioned, EGGVP supports the development of such guidance and will be happy to contribute in future discussions. A dialogue between the marketing authorisation holders and competent authorities should be planned; EGGVP calls these authorities to contact representative EU industry organisations when new guidelines are drafted, revision of Volume 9B takes place or the contents of the pharmacovigilance master file are proposed, so as to gather their input and proposals. It is paramount that the new pharmacovigilance rules and guidance are clear and easy to operate for all (regulators and industry) in order to allow predictability and effective implementation, while avoiding misinterpretation and increased burden for all.

It is also noted that all aspects of good pharmacovigilance practice are based on a functional Union pharmacovigilance database, for which the basis is a functional Union product database. Both databases should be implemented with a sufficient time for training courses before the new legislation will come in place so as to allow an effective implementation.

A SYSTEM TAILORED TO VETERINARY BUSINESSESS

The experience with volume 9B is generally and positively valued by veterinary marketing authorisation holders and as such EGGVP does not support deviating from it. Volume 9B is already in force for a long period and fits well the purpose for the veterinary sector.

EGGVP is concerned that the EMA advice is proposing a signal management system based on the system in place for human medicines. The veterinary and human medicines industries have a substantially different infrastructure, with a veterinary medicines market representing approximately 4% of the human medicines market. It is essential to acknowledge that the requirements for human medicinal products regulations do not fit the veterinary business scale. Not doing so will result in an enormous/disproportionate burden for the veterinary industry, with expenses related to administrative burden estimated nowadays at about 13% of total industry turnover; this is inadmissible in any context, but even more taking into account the slow return of investment for veterinary medicines.

Therefore, EGGVP does not support going in this direction. The new pharmacovigilance rules should be customized to the veterinary sector and so EGGVP would rather support the review of Volume 9B, by making the necessary adaptations.

EGGVP specific comments

SECTION 1: REPORTING AND RECORDING OF ADVERSE EVENTS AND THE SIGNAL MANAGEMENT PROCESS

- The recommendations set involve a substantial workload increase. After reading the provisions and EMA advices, the EGGVP members expect more tasks and administrative burden in the pharmacovigilance area.

- In brief, marketing authorisation holders will have to perform – annually –provision of sales data, calculation of incidence of adverse events, benefit-risk balance, monitoring / literature review and submission in the pharmacovigilance database. This is equivalent in terms of workload to a yearly PSUR. Considering that PSURs are nowadays submitted every 3 years for older medicines, this is a clear step back towards the objective of reducing unnecessary burden on the pharmacovigilance area.

SECTION 1.1: REPORTING AND RECORDING OF ADVERSE EVENTS

- As stated above, the main concern is that provisions are overall equivalent to a yearly PSUR, which results in much more workload for the marketing authorisation holders.

- EGGVP welcomes the risk based approach proposed. A vast majority of the marketing authorisations held by generic companies are on the market for many years, and publications and reports on new adverse events are very rare. For these products it is meaningless to perform weekly or even monthly searches in several databases for new literature. Therefore, the risk base approach is supported.

- In this regard, and so as to overcome the problem of excessive and disproportionate burden, both industry and competent authorities should search for a mutual agreement, whereas 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 signal evaluation for products with no / only few yearly reports should be envisaged).

  It should be noted that, in some of the EU Member States, this possibility is already in place under certain conditions:
  - Nihil sales, or
  - No incidence of AEs

  In such cases, certain national competent authorities agree receiving a simple declaration every 3 years. Similar provisions established in future pharmacovigilance guidance would be welcome.

- It is considered very positive that analytical tools are made available in the Union pharmacovigilance database. This would be helpful for signal management / detection specially if the database would include adverse events published in scientific literature, and

could probably allow performing signal management without the need of additional analytical tools, which is much welcome and in particular in support of small and medium sized companies. However, following the information that only basic functions of the database system will be ready in January 2022, there are concerns that analytical tools will not be available by then on the database, and so signal detection and management will demand huge investments, time and workload (especially if the requirements are set based on the system for human medicines, and depending on the guidance that will be developed).

- Under current pharmacovigilance system, the product name may often not be entered, as it is not in the database. A more simple process should be in place to enter the product name (ref. page 10, section 1.1.2.).

- Duplication of reports by multiple sendings shall be avoided and discussed with the authorities. Duplicates will be detected in a timely manner, if the competent authority or marketing authorisation holders are informed that a new report has been entered into the pharmacovigilance database (ref. page 11, section 1.1.3.).

- The EMA suggests that „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“. It should be clarified if this applies also to marketing authorisation holders (ref. page 12, section 1.1.5.).

- In line with the proposed rules, marketing authorisation holders shall focus the literature search on product name. However, according to experience from industry, this is of very little value as the search requests only bring a few articles where the product name is listed. This is particularly true for small and medium sized companies. A comprehensive literature search shall be done on a risk-based approach, considering the time a product is authorized and the number of adverse event reports linked to it. It is proposed that this is performed in greater time intervals.

- EGGVP welcomes that literature search shall be done on a risk based approach. Guidance is needed on the level of details, type and number of search terms and number of searches. EGGVP is willing to work together with the authorities in the process of finding the details of this guidance (ref. page 13, section 1.1.6.).

- Marketing authorisation holders should be responsible for monitoring signals for their own products (or groups of products) only. There must be no responsibility for marketing authorisation holders to review product literature for other products containing the same active ingredient (i.e. active substance or class of antibiotics).

- For to execute a signal management process, marketing authorisation holders should be aware of all adverse advent reports concerning their own products. It is assumed that marketing authorisation holders will receive from competent authorities the adverse event reports involving their products (same situation as today). The competent authorities should send the reports they receive from the veterinarians, pharmacovigilance centers or by any other means (i.e. literature) via the future reporting system, so that the marketing authorisation holder is aware of all adverse events reported in the time period.

- Marketing authorisation holders should not have an obligation to actively monitor the future reporting system for new adverse event reports to download.

- Not all signal management processes shall be executed in one month. A proposal should be given to distribute the active substances within the year as given in the harmonized data lock points (DLP) procedure. It is proposed to set new DLPs, and to keep the months as in the current triennia.

SECTION 1.2: PROVISION OF DATA FOR CALCULATION OF INCIDENCE ADVERSE EVENTS REPORTED TO THE PHARMACOVIGILANCE DATABASE

- It has to be clarified, from which database the annual sales are generated, so as to avoid double reporting of sales data. The EMA advice supports the reporting of the annual sales to the Union Product Database, and a further reporting of sales data and calculation of animals treated into the pharmacovigilance database. The annual provision of sales data (Union product database) and the calculation of animals treated (Union pharmacovigilance database) is a high burden, now performed every three years only, and is one of the highest time-consuming parts of a PSUR (besides the literature search and line listings), especially when the marketing authorisation holder has to ask distributors for their sales in the time period covered.

  It should be clearly recommended, which sales data are needed. There are 2 possibilities:

  1. To only report the sales from the company to each distributor in the member state, or

  2. To report the effective sales volumes of each distributor. To collect sales data from every distributor every year is a very high administrative burden, compared to the current 3-years-cycle.

- Besides the reporting of data on the Union product database and Union pharmacovigilance database, for antibiotics, whose consumption is of great matter of concern, the sales volume data is already provided in the ESVAC program. Sales data is also reported to many EU Member States individually and on an annual basis.

- Multiple reporting of sales data is of high concern and shall be avoided by all means. If visibility of the methodology for calculation is given, the sales data could be taken from the Union product database. Annual reporting in the Union product database will be calendar year, but it is not specified for the pharmacovigilance sales data. It is not possible for marketing authorisation holders to evaluate all products by signal management process and benefit-risk evaluation at one time i.e. January. Harmonized DLPs should be established.

- Mechanisms should be in place for marketing authorisation holders to report sales data only once. Appropriate IT solutions should be established (i.e. through common calculation formula to estimate the number of animals treated from the sales declared in the Union product database).

- The estimation of treated animals by marketing authorisation holders is problematic and inaccurate, since they can only deliver data based on assumptions, particularly for products intended for various species.
- It should also be noted that the only utility of providing such data 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.
- Data for a specific year will be reported in the next risk assessment, and introduced into the calculation. This will prevent wrong incidence calculation, as there might be several reports in one year for a product that had no reports in previous years.

SECTION 1.3: THE SIGNAL MANAGEMENT PROCESS DEFINED IN ARTICLE 4, PROVIDED FOR IN ARTICLE 81 AND EXPLAINED IN RECITAL 63 OF THE REGULATION

- A signal management process similar to the one established for pharmaceuticals for human use will involve a huge amount of work and a disproportionate administrative burden, and will certainly not suit the veterinary sector. Furthermore, the software developed for human pharmaceuticals is very sophisticated and expensive. Human medicine marketing authorisation holders must look up for articles every week, and therefore most companies have an external service providers responsible to perform the searches by automatic search in several databases. Having by far less resources, this will not be possible for veterinary companies.
- Furthermore, with human signal management process, industry performs searches based on product name, but for generic veterinary marketing authorisation holders this would result in very few / no results.
- Therefore, EGGVP does not support going in this direction. EGGVP would rather support the review of Volume 9B, and make the needed adaptations.
- The EMA advice states that, in order to avoid duplication of efforts, a work-sharing process for evaluation at Union level. This will probably give a chance for to perform benefit-risk evaluation for different active substances at different time points of the year. Also a risk-based approach will be considered in the guideline. These may be positive achievements (ref. pages 16 and 17).

SECTION 2: PHARMACOVIGILANCE COMMUNICATION

- The fact that alerts will be reported though the Union pharmacovigilance database is welcome. This will support the centralization of information and will avoid duplications of information in several systems. It is also positive that marketing authorisation holders will be included in the alerts/ communication.

- Nonetheless, all aspects given in the good pharmacovigilance practice are based on a functional Union pharmacovigilance database, for which the basis is a functioning Union product database. Both databases should be implemented with a sufficient time for training courses before the new legislation will be in place.
- The Union product database should be prioritized, and enough resources shall be guaranteed to ensure full and timely functionality.
- The link to an electronic version of the actual SPC (ref. page 22) will involve high resources (administrative and financial) from marketing authorisation holders, while its value is questionable. It carries the danger that changes in part II with a revised formulation are implemented on lots in the market, which do not carry these changes, e.g. change in the preservatives, which might cause toxic effects in some animal species. It should also be clarified if variations will be needed to implement the link in the product information literature. Furthermore, transition times for implementation should be given.

SECTION 3: PHARMACOVIGILANCE INSPECTIONS

- In general, industry reports positive experiences with the pharmacovigilance inspections done by national competent authorities. EGGVP believes there should be no multinational inspection teams, as the decision if the pharmacovigilance system is adequate is to be done by national competent authorities (as it is in case with the GMP certificate). It can be considered if such a certificate will be issued by the authorities following inspection and can be placed into the file for application of a marketing authorisation (as the GMP certificate). The first pharmacovigilance system certificate can be issued on the basis on the results of the latest inspection.
- For idiomatic/language reasons, EGGVP members prefer to deal with national inspectors from their own Member State where the company is located.
- In cases where an EU / EMA pharmacovigilance inspection has taken place, it should have EU validity/coverage. As such, additional national inspections should not be carried on top, as these are regarded as unnecessary and only adding extra burden. It would be of benefit if any inspection, also performed by national competent authorities, shall have validity for the other EU countries (including countries of the EU-regulatory network such as Norway).
- In this regard, the recommendation of work-sharing to avoid duplications of inspections is seen as a positive achievement.
- It is also welcome that the frequency and scope of the inspections should be adjusted (reduced or increased) based on a risk- based approach, and that 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.