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Committee for Medicinal Products for Veterinary Use

Scientific recommendation for implementing measures under Article 77(6) of Regulation (EU) 2019/6 on veterinary medicinal products regarding the pharmacovigilance system master file

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Introduction

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

- the experience gained with the application of the current 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 experience gained by inspections of pharmacovigilance systems for veterinary medicinal products;
- the format and content of the current Detailed Description of the Pharmacovigilance System (DDPS);
- the experience gained with the pharmacovigilance system master file (PSMF) in human medicine and with the application of the Guideline on good pharmacovigilance practices (GVP) Module II – Pharmacovigilance system master file and the content of pharmacovigilance system master file as detailed in Article 2 of Commission Implementing Regulation (EU) No 520/2012;
- the changes foreseen in Regulation (EU) 2019/6 from the current system of adverse event reporting and Periodic Safety Update Reports to adverse event reporting and signal management process.

The Committee for Medicinal Products for Veterinary Use (CVMP) formed an expert group to prepare the scientific recommendations. The group 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.

In view of the applicability of pharmacovigilance system to all products authorised in the EU independent of the route of authorisation and the responsibilities of the competent authorities in the inspection of the system master files it was considered appropriate to consult the Coordination group for Mutual recognition and Decentralised procedures (veterinary), CMDv on the advice.

The expert group submitted their draft recommendations to the CMDv, and the 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.

Overview of recommendations, considerations and rationale

The concept of the pharmacovigilance system master file has been introduced in the veterinary sector for the first time with Regulation (EU) 2019/6. It is intended to be a detailed description of the pharmacovigilance system of the marketing authorisation holder with respect to one or more of its authorised veterinary medicinal products that is not part of the marketing authorisation application dossier. The recommendations made for inclusion in the implementing act are considered to be key factors for ensuring a robust and efficient pharmacovigilance system.

In order to ensure that the system is adaptable and flexible to the needs of all stakeholders, further details required for full and appropriate implementation of the legal requirements are foreseen to be described in guidelines.

General principles

Regulation (EU) 2019/6 requires that marketing authorisation holders ensure that all their products are covered by a pharmacovigilance system described in a pharmacovigilance system master file. A pharmacovigilance system may cover one or more products, but for each product the marketing authorisation holder shall not have more than one pharmacovigilance system master file, as required by Article 77(2). The recommendations aim at discouraging multiple pharmacovigilance systems, unless it is appropriate and justified. Multiple pharmacovigilance systems may reduce the pharmacovigilance system oversight and make the system less efficient in the fulfilment of pharmacovigilance obligations and create an increase in administrative burden for both the marketing authorisation holder and the national competent authorities. Minimum requirements for the content, format and maintenance of the pharmacovigilance system master file (main part and annexes), and its summary are proposed. In accordance with Article 79(6) of the Regulation, the competent authority or the Agency, as applicable, may at any time request the marketing authorisation holder to submit a copy of the pharmacovigilance system master file; it is considered essential that an up-to-date version of the pharmacovigilance system master file is available upon request. The requirement for a detailed record of any change to the elements in the body of the pharmacovigilance system master file will enhance tracking of important changes in the pharmacovigilance system and will facilitate version control.

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

Pharmacovigilance system master file location and inspections

The pharmacovigilance system master file location, in accordance with Article 126(4) of the Regulation, defines the Member State which conducts the pharmacovigilance inspection of the concerned pharmacovigilance system master file (proposed to be named as the Supervisory Authority). The required information on the location of the pharmacovigilance system master file is a physical office address of the marketing authorisation holder or a contracted third party. Where the pharmacovigilance system master file is held in electronic form, the location stated must be a site in the EU, where the data stored can be directly accessed, also for inspection or audit. The pharmacovigilance system master file shall be located either at the site where the main pharmacovigilance activities of the marketing authorisation holder in the EU are performed or at the site in the EU where the qualified person responsible for pharmacovigilance operates. The marketing authorisation holder should have an appropriate rationale for the decision to locate the pharmacovigilance system master file at a specific site. In the situation where the main pharmacovigilance activities take place outside the EU, the location should default to the site where the qualified person responsible for pharmacovigilance operates.

Description of the quality system for the performance of pharmacovigilance activities

Noting that the Regulation does not include reference to quality management systems, it is considered essential that the implementing act requires that the pharmacovigilance system master file includes a description of the quality system for the performance of pharmacovigilance activities, including corrective and preventive action plan management and change management. The pharmacovigilance system master file shall also include, in the annexes, a list of all completed and scheduled audits as an important tool for pharmacovigilance system oversight (to promote planning and conduct of audits by marketing authorisation holders). In the annexes, completed audits associated with unresolved significant deviations should be identified and associated corrective and preventative action(s) should

be documented. Including this information in the pharmacovigilance system master file would make the information readily available to inspectors.

Delegation of pharmacovigilance activities

When delegating any activities concerning the pharmacovigilance system and its master file, the marketing authorisation holder retains ultimate responsibility for the pharmacovigilance system, submission of information about the pharmacovigilance master file location, maintenance of the pharmacovigilance system master file and making it available to competent authorities upon request. Detailed written agreements describing the roles and responsibilities for pharmacovigilance system master file content, submission and management, as well as roles and responsibilities for the conduct of pharmacovigilance in accordance with the legal requirements, should be in place.

Summary of the pharmacovigilance system master file

Article 8(1c) of the Regulation requires a summary of the pharmacovigilance system master file to be submitted as part of the application dossier, and the recommendations propose to keep the information to the minimum required, including a statement from the applicant or the future marketing authorisation holder that they have the means to fulfil their pharmacovigilance obligations. The marketing authorisation holder statement wording from Volume 9B was used as a basis for the statement in the summary of the pharmacovigilance system master file.

In addition, it is recommended that the Member States and the Agency have continuous access to the information proposed for the summary, name and contact details of the qualified person responsible for pharmacovigilance as the contact point for inspections (Article 78(2)) and pharmacovigilance system master file reference and location, and any update to those, as this information is essential for risk-based inspection planning (Article 123(3)).

Points for further consideration

Further considerations and discussions among Member States and the Agency are required to develop an approach to dealing with major changes in the pharmacovigilance system that are not part of the pharmacovigilance system master file summary (e.g. change in the marketing authorisation holder's pharmacovigilance database, subcontracting or change in subcontracting pharmacovigilance activities) but that may affect risk-based inspection planning. These discussions should elaborate the essential information required and the process to collect this required information. Options currently discussed include the further improvements of the functionalities of the Union pharmacovigilance database, as referred to in Article 74, to facilitate the communication of major changes in the pharmacovigilance system to the Member States and the Agency.

Pharmacovigilance system master file

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1. General requirements for the pharmacovigilance system master file

1. The information in the pharmacovigilance system master file shall be accurate and reflect the current pharmacovigilance system in place.
2. The pharmacovigilance system master file shall comprise a main part with basic information required to describe the pharmacovigilance system, and annexes containing information that may be subject to frequent change and which is useful for the pharmacovigilance system oversight, audits and inspections.
3. All veterinary medicinal products shall be covered by a pharmacovigilance system master file, in accordance with Regulation (EU) 2019/6, Articles 77(1) and 77(2).

The marketing authorisation holder may, where appropriate and justified, use separate pharmacovigilance systems for different medicinal products. Each such system shall be described in a separate pharmacovigilance system master file.

2. Content of the main part of the pharmacovigilance system master file

The pharmacovigilance system master file shall contain at least the following elements:

1. its reference number;
2. the address where the pharmacovigilance system master file is located for the purpose of pharmacovigilance inspections in accordance with Article 126(4) of Regulation (EU) 2019/6;
3. the following information relating to the qualified person responsible for pharmacovigilance:
    a. name and contact details of the qualified person responsible for pharmacovigilance,
    b. a description of the responsibilities, demonstrating that the qualified person responsible for pharmacovigilance has oversight over the pharmacovigilance system and has sufficient authority in order to promote, maintain and improve compliance with pharmacovigilance tasks and responsibilities; if necessary, a description of the measures 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,
    c. where the qualified person responsible for pharmacovigilance has not completed veterinary surgeon training 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, documentation on the marketing authorisation holder arrangements to ensure that the qualified person responsible for pharmacovigilance is assisted by a veterinary surgeon who is available on a continuous basis;
4. description of back-up arrangements that apply in the absence of the qualified person responsible for pharmacovigilance;
5. a detailed description of the organisational structure for all pharmacovigilance activities of the marketing authorisation holder, including the position of the qualified person responsible for pharmacovigilance within the organisation. Marketing authorisation holders belonging to the same parent company or group of companies have to be taken as one entity;

6. a description of the location of, functionality of and operational responsibility for recording systems and databases used to receive, collate, record and report safety information and a summary of the assessment of their fitness for purpose;

7. a description of data handling and recording and of the process used for each of the following pharmacovigilance activities:

    a. collection, collation, assessment, quality monitoring, reporting, and archiving of all suspected adverse events brought to the attention of the marketing authorisation holder in the EU or in a third country,

    b. the signal detection and management process in place and its continuous assessment,

    c. the continuous monitoring of the risk-benefit balance of the veterinary medicinal product(s), the result of that monitoring and the decision-making process for taking appropriate measures,

    d. operation of the risk management system(s) and the monitoring of the outcome of risk minimisation measures,

    e. communicating safety concerns and safety variations to the marketing authorisation to veterinarians and other healthcare professionals and the general public;

8. a description of the training management for pharmacovigilance activities;

9. a description of the quality management system for pharmacovigilance activities including:

    a. a description of the various types of documents, written policies and procedures that must be documented for all pharmacovigilance activities and tasks,

    b. a brief description of the responsibilities for quality assurance auditing of the pharmacovigilance system including, where appropriate, auditing of subcontractors,

    c. a brief description of corrective and preventive action plan management and change management;

10. a description of the system in place to ensure that all relevant pharmacovigilance documents are archived, so as to ensure their accurate and ready retrieval throughout the period for record-keeping. Pharmacovigilance data, and documents relating to individual authorised veterinary medicinal products, shall be retained as long as the product is authorised or registered and for at least ten years after the marketing authorisation has ceased to exist. However, the documents shall be retained for a longer period where Union law or national law so requires;

11. where applicable, a description of the activities or services subcontracted by the marketing authorisation holder to fulfil pharmacovigilance obligations.

3. Content of the annexes to the pharmacovigilance system master file

The pharmacovigilance system master file shall have annexes containing the following documents:

1. a list of all veterinary medicinal products covered by the pharmacovigilance system master file, including the international non-proprietary name (INN) of the active substance(s), the Member State(s) in which the product is authorised or registered, type of procedure for authorisation and authorisation number;

2. a curriculum vitae of the qualified person responsible for pharmacovigilance, indicating that the qualified person is appropriately qualified and trained in order to fulfil the responsibilities and tasks of the position and the proof of registration with the pharmacovigilance database;
3. details on back-up arrangements and, when applicable, the veterinary surgeons, assisting the QPPV including the contact details and curriculum vitae of persons involved;
4. a list of written policies and procedures of the pharmacovigilance system;
5. a list of existing contracts and agreements with the third parties referred to in the section "Subcontracting", specifying the tasks that have been contracted out, the product(s) and territory(ies) concerned, including the contact details of the contractors with pharmacovigilance obligations, where applicable;
6. a list of the tasks of the qualified person responsible for pharmacovigilance referred to in Article 78 of Regulation (EU) 2019/6 that have been totally or partially outsourced;
7. a list of other pharmacovigilance system master files held by the same marketing authorisation holder, where applicable;
8. a list of local or regional representatives, for the purpose of receiving reports of suspected adverse events, including their contact details, responsibilities and territories, where applicable;
9. a list of performance indicators to monitor the performance of the pharmacovigilance system, as applicable;
10. a list of all scheduled and completed audits. Audits associated with unresolved significant deviations should be identified and associated corrective and preventative action(s) should be documented;
11. a logbook or version history containing the information detailed in the section "Format of the pharmacovigilance system master file".

4. Content of the summary of the pharmacovigilance system master file

The summary of the pharmacovigilance system master file shall contain the following items:

1. a signed statement from the applicant and the qualified person for pharmacovigilance to the effect that the applicant has their services available as qualified person for pharmacovigilance and has the necessary means to fulfil the tasks and responsibilities in Section 5 Pharmacovigilance of Regulation (EU) 2019/6;
2. pharmacovigilance system master file reference number;
3. qualified person responsible for pharmacovigilance name, contact details and place of operation;
4. pharmacovigilance system master file location.

5. Maintenance of the pharmacovigilance system master file

1. The marketing authorisation holder shall keep the pharmacovigilance system master file, including its annexes and summary, up to date and, where necessary, revise it to take account of experience gained, of technical and scientific progress and of amendments to Regulation (EU) 2019/6.

2. The pharmacovigilance system master file and its annexes shall be subject to version control and indicate the date(s) when it was last updated.

3. After the system as described in the pharmacovigilance system master file has been formally terminated, the marketing authorisation holder shall arrange for the elements referred to in the section "Content of the main part of the pharmacovigilance system master file" to be kept for at least ten years.

4. The marketing authorisation holder of a veterinary medicinal product shall notify immediately the Agency and the relevant competent authority of any change in the summary of the pharmacovigilance system master file by submitting a relevant variation application. Major changes of the pharmacovigilance system affecting risk-based controls should be communicated to the Member States in accordance with relevant guidance.

6. Format of the pharmacovigilance system master file

1. Pharmacovigilance system master file shall be accurate, complete and legible. Where appropriate, information may be provided in the form of charts or flow diagrams. All documents that form part of the pharmacovigilance system master file shall be indexed to ensure their accurate and ready retrieval throughout the period for record-keeping.

2. The pharmacovigilance system master file may be stored in electronic form, provided that the media used for storage remain readable over time and searchable and a clearly arranged printed copy can be made available for audits and inspections.

3. The marketing authorisation holder shall record in the logbook referred to in point 11 of the section "Content of the annexes to the pharmacovigilance system master file" any alteration of the content of the pharmacovigilance system master file made within the last five years. The marketing authorisation holder shall indicate in the logbook the date, the person responsible for the alteration and, where appropriate, the reason for the alteration.

4. The particulars and documents of the pharmacovigilance system master file should be presented in accordance with relevant guidance.

7. Subcontracting

The marketing authorisation holder may subcontract pharmacovigilance tasks to third parties but shall nevertheless retain full responsibility for all its pharmacovigilance obligations and ensure that these are fulfilled as laid down in the Regulation (EU) 2019/6 and shall retain full responsibility for the completeness and accuracy of the pharmacovigilance system master file.

8. Location and availability of the pharmacovigilance system master file

1. The pharmacovigilance system master file shall be located either at the site where the main pharmacovigilance activities of the marketing authorisation holder in the EU are performed or at the site in the EU where the qualified person responsible for pharmacovigilance operates. This unique pharmacovigilance master file location and any changes to the location shall be notified to the competent authority(ies) and the Agency by submitting the relevant variation.

2. The marketing authorisation holder shall ensure that the qualified person for pharmacovigilance has permanent access to the pharmacovigilance system master file.

3. The pharmacovigilance system master file shall be permanently and immediately available for inspection at the site where it is kept.
4. Where the pharmacovigilance system master file is kept in electronic form, in accordance with point 2 of the section "Format of the pharmacovigilance system master file", it is sufficient that the data stored in electronic form is directly available at the site where the pharmacovigilance system master file is kept.
5. Any competent authority or the Agency, as applicable, may at any time request the marketing authorisation holder to submit an up-to-date copy of the pharmacovigilance system master file with its annexes, in accordance with Article 79(6) of Regulation (EU) 2019/6.