COMMISSION IMPLEMENTING REGULATION (EU) 2021/1281

of 2 August 2021

laying down rules for the application of Regulation (EU) 2019/6 of the European Parliament and of the Council as regards good pharmacovigilance practice and on the format, content and summary of the pharmacovigilance system master file for veterinary medicinal products

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 laying down Community Regulation on veterinary medicinal products and repealing Directive 2001/82/EC ([1]), and in particular Article 77(6) thereof,

Whereas:

(1) Good pharmacovigilance practice should cover all activities across the full life-cycle management of veterinary medicinal products in relation to safety authorised in accordance with Article 5 of Regulation (EU) 2019/6 or registered in accordance with Article 86 of that Regulation. Non-compliance with pharmacovigilance obligations could have a potentially serious impact on public and animal health and on the environment.

(2) Marketing authorisation holders should respect good pharmacovigilance practice by implementing a robust and efficient pharmacovigilance system, supported by a quality management system covering all pharmacovigilance activities, including a risk management system covering all procedures and processes necessary to optimise safe use of their veterinary medicinal products. The quality management system should be updated regularly and checked by audits at risk-based intervals, and should include provisions to identify corrective and preventive actions and manage and document corresponding changes to those actions.

(3) In order to facilitate the enforcement of pharmacovigilance obligations, the marketing authorisation holder should retain full responsibility for all pharmacovigilance obligations subcontracted to third parties.

(4) As an important part of a marketing authorisation holder's quality management system, all information on pharmacovigilance data, including standard procedures, should be saved and preserved in a document management system. The document management system should include a record management system to process safety data.

(5) 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 balance of a product. Marketing authorisation holders should, within 30 days, record all adverse event reports collected for all their veterinary medicinal products in the Union pharmacovigilance database in order to enable analysis of information received over the full life-cycle of a product.

(6) Standard terminology in the field of medical science should be used in harmonising the exchange of pharmacovigilance information to improve consistency of data related to adverse event reporting.

([1]) OJ L 4, 7.1.2019, p. 43.

(7) The calculation of incidence of adverse events should allow for the comparison of different products, product groups or different time periods for the same product.

(8) The signal management process should enable continuous monitoring of the benefit-risk balance of a veterinary medicinal product. It should therefore be a core element of the pharmacovigilance system, allowing appropriate measures to be taken, in accordance with Article 77(4) of Regulation (EU) 2019/6.

(9) Communication of information about the safe and effective use of veterinary medicinal products should support appropriate use and should be considered throughout the risk management process.

(10) The pharmacovigilance system master file should contain all relevant information and documents concerning pharmacovigilance activities, including information on tasks that have been subcontracted to third parties. That information should contribute to the appropriate planning and conduct of audits by marketing authorisation holders and the supervision of pharmacovigilance activities by the qualified person responsible for pharmacovigilance. Furthermore, that information should enable competent authorities to verify compliance concerning all aspects of the system.

(11) Marketing authorisation holders should ensure that they and any third party carrying out pharmacovigilance activities in relation to their veterinary medicinal products make the necessary preparations in order to facilitate controls or inspections by the national competent authorities or the European Medicines Agency.

(12) This Regulation should apply from 28 January 2022 in accordance with Article 153(1) of Regulation (EU) 2019/6.

(13) The measures provided for in this Decision are in accordance with the opinion of the Standing Committee on Veterinary Medicinal Products,

HAS ADOPTED THIS REGULATION:

CHAPTER 1

GENERAL PROVISIONS AND PHARMACOVIGILANCE SYSTEM

Article 1

Definitions

For the purposes of this Regulation, the following definitions shall apply:

(a) ‘quality management system’ means a formalised system that provides for comprehensive processes, procedures, and responsibilities for achieving quality policies and objectives to coordinate and direct an organisation’s activities and improve its effectiveness and efficiency in this regard on a continuous basis;

(b) ‘performance indicator’ means an item of information collected at regular intervals to monitor the performance of a system;

(c) ‘signal’ means information that arises from one or multiple sources, including observations and experiments, which suggests a potentially new causal association, or a new aspect of a known causal association between an intervention and an adverse event or a set of related adverse events, that is judged likely to justify further investigation of possible causality.

Article 2

Pharmacovigilance system

1. The marketing authorisation holder's pharmacovigilance system established and maintained in accordance with Article 77(1) of Regulation (EU) 2019/6 shall meet the requirements laid down in this Regulation.

2. The marketing authorisation holder shall ensure that the pharmacovigilance system:

(a) is fully functional;

(b) is covered by a comprehensive quality management system as provided for in Articles 4 to 9 of this Regulation;

(c) includes a risk management system covering all procedures and processes necessary to optimise safe use and monitor benefit-risk balance of their veterinary medicinal products;

(d) sets out clearly the roles, responsibilities and required tasks for all parties involved in operating the system;

(e) provides for proper control over the system and ensures that, when needed, the necessary changes to the system to improve its operation can be carried out;

(f) is clearly and unambiguously documented in the pharmacovigilance system master file.

3. Marketing authorisation holders shall ensure that the qualified person responsible for pharmacovigilance referred to in Article 77(8) of Regulation (EU) 2019/6 has sufficient control over the pharmacovigilance system in order to promote, maintain and improve compliance with Article 78 of that Regulation. They shall ensure that there is an appropriate procedure in place to identify and deal with any conflicts of interest of the qualified person responsible for pharmacovigilance.

4. Marketing authorisation holders shall have a sufficient number of competent and appropriately qualified and trained personnel working for them in the performance of pharmacovigilance activities.

5. All persons involved in the procedures and processes of the pharmacovigilance system established for the performance of pharmacovigilance activities shall ensure the proper functioning of the system when fulfilling their role for the marketing authorisation holder.

6. Marketing authorisation holders shall establish and document back-up procedures to ensure business continuity with regard to the fulfilment of pharmacovigilance obligations.

7. Marketing authorisation holders shall retain full responsibility for all pharmacovigilance obligations subcontracted to third parties as laid down in Regulation (EU) 2019/6 and in this Regulation.

Article 3

Qualified person responsible for pharmacovigilance

1. The qualifications and training of the qualified person responsible for pharmacovigilance referred to in Article 77(8) of Regulation (EU) 2019/6 shall include documented experience in pharmacovigilance.

2. The qualified person responsible for pharmacovigilance shall have completed veterinary surgeon training in accordance with Article 38 of Directive 2005/36/EC of the European Parliament and of the Council ([2]). Where such training has not been completed, marketing authorisation holders shall make arrangements to ensure that the qualified person responsible for pharmacovigilance is assisted by a veterinary surgeon on a continuous basis. That assistance shall be duly documented.

([2]) Directive 2005/36/EC of the European Parliament and of the Council of 7 September 2005 on the recognition of professional qualifications (OJ L 255, 30.9.2005, p. 22).

CHAPTER 2

QUALITY MANAGEMENT SYSTEM

Article 4

Quality management system for pharmacovigilance

1. Marketing authorisation holders shall establish and implement an adequate and effective quality management system for the performance of their pharmacovigilance activities.

2. The quality management system shall be described in the pharmacovigilance system master file.

3. Marketing authorisation holders shall ensure that the quality management system includes detailed policies, processes and procedures on document management, training, audits, and change management covering the activities in accordance with Articles 5 to 9. Those policies, processes and procedures shall provide for a review of the quality management system at regular risk-based intervals, based on pre-defined criteria.

4. Marketing authorisation holders shall ensure that the quality management system includes detailed policies, processes and procedures for the record management system and data collection in accordance with Articles 10 to 15, for the following pharmacovigilance activities:

(a) initial recording of any suspected adverse event;

(b) collection of additional data;

(c) collation of reports of suspected adverse events and additional data;

(d) data handling other than mentioned in points (a) to (c);

(e) evaluation of data;

(f) monitoring of quality, integrity and completeness of all information registered in the pharmacovigilance system including information reported to the Union pharmacovigilance database and management of duplicates;

(g) recording of any adverse event in the Union pharmacovigilance database;

(h) archiving of all relevant documents.

5. Marketing authorisation holders shall ensure that the quality management system includes detailed policies, processes and procedures for risk management, monitoring of the benefit-risk balance, signal management and communication to all relevant stakeholders in accordance with Articles 16 to 20.

6. Marketing authorisation holders shall ensure that the quality management system includes detailed policies, processes and procedures for the maintenance and availability of the pharmacovigilance system master file in accordance with Articles 24 and 25.

7. Marketing authorisation holders shall clearly define the roles and responsibilities of those persons involved in pharmacovigilance activities and in documentation in accordance with paragraphs 3 to 6 of this Article.

8. Marketing authorisation holders shall set up a quality management system using the following:

(a) quality planning: establishing structures, integrated planning and consistent processes;

(b) quality adherence: carrying out tasks and responsibilities in accordance with quality requirements;

(c) quality control and assurance: monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are implemented;

(d) quality improvements: correcting and improving the structures and processes where necessary.

Article 5

Document management system

1. Marketing authorisation holders shall set up and maintain a document management system to keep all documents related to pharmacovigilance activities. Those documents shall be archived and indexed to enable accurate and easy accessibility throughout the period of record-keeping.

2. Documents shall be subject to version control, as appropriate.

3. Documents and pharmacovigilance data relating to individual authorised veterinary medicinal products shall be retained as long as the product is authorised and for 5 years after the marketing authorisation ceases to be valid.

Article 6

Training

1. All personnel involved in the performance of pharmacovigilance activities shall receive initial and continuous training for their role and responsibilities in relation to the activities mentioned in Article 4, paragraphs 3 to 6, also including activities related to clinical trials, technical product complaints, standards, sales and marketing.

2. Marketing authorisation holders shall have a training management system in place for maintaining and developing the competences of their personnel. Information on training plans and records for pharmacovigilance activities and a reference to their location shall be kept in Annex IV, point (iv) to the pharmacovigilance system master file.

Article 7

Performance indicators

Marketing authorisation holders shall use relevant performance indicators to continuously monitor the performance of pharmacovigilance activities and the outcome of risk minimisation measures. They shall keep a list of those performance indicators including the reason why they have been chosen and a description on how to use them in Annex IV, point (iii) to the pharmacovigilance system master file.

Article 8

Audits

1. Marketing authorisation holders shall perform audits of the pharmacovigilance system at regular risk-based intervals to ensure that it complies with the requirements set out in this Regulation and to determine its effectiveness. The audits shall be planned to cover all pharmacovigilance activities for a defined period and verify their conformity with the policies, processes and procedures of the quality management system. They shall be conducted by individuals who have no direct involvement in or responsibility for the matters or processes audited.

2. Any third party contracted to carry out pharmacovigilance activities in whole or in part, on behalf of or in conjunction with marketing authorisation holders, shall accept to be audited by or on behalf of marketing authorisation holders.

3. Marketing authorisation holders shall draw up a risk-based schedule for auditing. The process for risk-based planning shall be described and the rationale for the risk-based schedule shall be documented. A list of scheduled and completed audits, including outstanding critical and major findings, shall be documented in Annex IV, point (ii) to the pharmacovigilance system master file.

Article 9

Corrective and preventive action and change management

1. Marketing authorisation holders shall have a process in place for managing corrective and preventive actions, to mitigate any deviations detected in audits, daily operational work and findings from inspections. Associated corrective and preventative actions shall be documented for the last 5 years.

2. Corrective and preventive action plans requested by the competent authority shall document in writing an effective process, systematically addressing and minimising identified risk or defects. It shall include root cause analysis, address clear possible corrective and preventive measures, address timelines for action, and communication to relevant stakeholders.

3. Marketing authorisation holders shall monitor and assess the effectiveness of corrective and preventive actions. Any changes associated with those actions shall be evaluated.

4. Change management shall provide for a controlled process of change, including monitoring and documenting the effectiveness of the corrective or preventive actions and communication to relevant stakeholders.

CHAPTER 3

RECORD MANAGEMENT SYSTEM, DATA COLLECTION AND MONITORING

Article 10

Record management system

1. The document management system referred to in Article 5 shall include a record management system for receiving, recording, collating and assessing information on adverse events and for recording safety information.

2. The description of the record management system for recording adverse events and safety information in Section D of the pharmacovigilance system master file shall include the following information:

(a) type of record management system used for adverse event reports, including the name of the database used, if applicable;

(b) location where the record management system is kept;

(c) description of functionality of the record management system;

(d) operational responsibility of the personnel responsible for the record management system;

(e) summary of the assessment of its fitness for purpose.

3. Marketing authorisation holders may use the Union pharmacovigilance database as their electronic record management system for recording adverse events. In that case, Section D of the Pharmacovigilance system master file shall indicate that the record management system being used is the Union pharmacovigilance database.

Article 11

Suspected adverse events

Marketing authorisation holders shall collect and maintain detailed records of all suspected adverse events from all sources within or outside the Union in accordance with Article 77(1) of Regulation (EU) 2019/6. Those records shall include post-marketing surveillance studies and literature relating to their veterinary medicinal products, and suspected adverse events concerning use of their veterinary medicinal products outside the terms of the marketing authorisation.

Article 12

Recording of adverse events

1. Information concerning suspected adverse events shall be recorded and coded using internationally agreed standards. The latest version of the standards shall be used in line with the specified implementation dates.

2. Records of adverse events shall include at least the following:

(a) an identifiable reporter or source (including the country code);

(b) details of identifiable animals, humans or environment;

(c) veterinary or human medicinal product names;

(d) details on the adverse events.

3. Where the name of the product is not included in the initial report from the primary source, marketing authorisation holders shall make reasonable efforts to obtain the name or at least part of the trade name of the medicinal product concerned. If neither the name nor the trade names are known and cannot be obtained, the name of the active substances shall be recorded in the record management system.

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

Article 13

Adverse event recording in the Union pharmacovigilance database

1. Marketing authorisation holders shall record adverse events in the Union Pharmacovigilance database.

2. A language customary in the field of medical science shall be used to record non-coded information in the Union pharmacovigilance database, including such information related to adverse events originating outside the Union.

3. Marketing authorisation holders shall regularly monitor the scientific literature to identify any adverse events concerning their veterinary medicinal products. The method for monitoring literature and the frequency with which monitoring is conducted shall take into account the risk-based approach. It shall at least cover the following topics: active substance, type of product, the stability in number and incidence of reports observed over time on the market and the stability of the pharmacovigilance profile.

Article 14

Provision of additional data

1. To enable comprehensive analysis of adverse event reports from third countries, marketing authorisation holders shall record in the Union product database the corresponding product names and authorisation numbers for the same product or, if the same product is not authorised in the Union, for a similar product authorised in the Union, as defined in the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) Guideline 24 ([3]). Marketing authorisation holders shall update the information when necessary.

2. The total number of animals displaying an adverse event during a defined period of time, multiplied by 100 and divided by an estimate of the number of animals treated during that period, shall provide the incidence of reported adverse events. To calculate the estimated number of animals treated from the information on volume of sales required under Article 58(12) of Regulation (EU) 2019/6, marketing authorisation holders shall identify and provide a factor to the Union

([3]) https://www.ema.europa.eu/en/documents/scientific-guideline/vich-gl24-guideline-pharmacovigilance-veterinary-medicinal-products-management-adverse-event-reports_en.pdf

product database for each of their veterinary medicinal products according to country, target species and pack size. According to the posology of the product, the factor will determine how many animals can be treated with one package of a given pack size, regardless of the formulation. To calculate the incidence for adverse event reports from third countries via the estimated number of animals treated, marketing authorisation holders shall provide information on volume of sales for each of their veterinary medicinal products, combined for all third countries according to target species, and in regard to the same or a comparable pack size.

3. The Agency shall publish guidance on the mathematical formula to calculate the factor. Marketing authorisation holders shall record their assumptions on distribution of sales per target species and treatment regimen per target species that they use for the calculation of the factor in the pharmacovigilance system master file. Marketing authorisation holders shall update the factor when necessary.

Article 15

Post-marketing surveillance studies

1. Post-marketing surveillance studies may be conducted by marketing authorisation holders on their own initiative or shall be conducted by marketing authorisation holders on request of a competent authority or the Agency in accordance with Article 76(3) and (4) of Regulation (EU) 2019/6.

2. Voluntary post-marketing surveillance studies shall be notified to the responsible competent authority or the Agency immediately after initiation. The marketing authorisation holder shall submit the protocol and the final report within one year after completion of the data collection to the competent authority or the Agency, as applicable.

3. For a requested post-marketing surveillance study, the marketing authorisation holder shall submit the draft study protocol to the competent authority or the Agency who requested the study, as applicable, for approval at the latest two months before the trial is conducted.

4. The marketing authorisation holder shall notify the competent authority of the territory in which the post-marketing surveillance study is conducted, where that competent authority did not request the study.

5. The marketing authorisation holder shall submit the study protocol, the summary of the final study report and the final study report after finalisation of the study to the competent authority or the Agency who requested the post-marketing surveillance study, as applicable, and to the competent authority of the territory in which the study was conducted.

6. The marketing authorisation holder shall submit all relevant documents in a language customary in the field of medical science, except for studies to be conducted for veterinary medicinal products that are authorised only in one Member State. For those studies, the marketing authorisation holder shall provide a translation of the title, the summary of the study protocol and a summary of the final report of the study in a language customary in the field of medical science.

7. The marketing authorisation holder shall ensure that all information concerning the study is handled and stored in such a way that it can be correctly reported, interpreted and verified. The marketing authorisation holder shall ensure that the analytical dataset and statistical programmes used to generate the data contained in the final report of the study are stored electronically and are available for audits and inspections upon request of the competent authority or the Agency, as applicable.

Article 16

Risk management system

1. Marketing authorisation holders shall ensure that the pharmacovigilance system includes a risk management system to take appropriate action to minimise identified risks, when necessary.

2. The risk management system shall include a process for monitoring the benefit-risk balance of products and performing signal management. It shall also include a communication system in accordance with Article 20.

3. Marketing authorisation holders shall ensure continuous assessment and document the risk management measures and the outcome of risk minimisation measures in the pharmacovigilance system master file.

Article 17

Signal management process

1. The signal management process shall consist of at least pharmacovigilance processes of signal detection, prioritisation, validation, assessment and documentation of outcome.

2. Where marketing authorisation holders are responsible for the same or a similar veterinary medicinal product as defined in the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) Guideline 24 ([4]), authorised in different Member States through different authorisation procedures, the signal management process may be performed at active substance level for all the products combined.

3. Marketing authorisation holders shall perform signal management using a risk-based approach and monitor the data with a frequency proportionate to the identified risk. The risk-based approach shall take into account the following topics: type of product, length of time on the market and stability of the pharmacovigilance profile, identified and potential risks and the need for additional information. The risk-based approach shall be applied to determine the methodology, extent and frequency of the signal management process and the rationale shall be documented.

4. Signal assessment shall analyse and evaluate the potential impact of a signal on the benefit-risk balance of a product and shall allow for relative comparison between different products or product groups, including analysis at active substance level and stratified analyses.

5. The Agency shall publish guidance on best practice for signal management.

6. The outcome of the signal management process shall be recorded and the rationale shall be kept ready for inspection.

7. Marketing authorisation holders shall conduct at least one signal detection analysis per year for each of their active substances or products in the Union pharmacovigilance database.

8. Marketing authorisation holders using the Union pharmacovigilance database as their record management system for adverse event reports shall perform signal management in the Union pharmacovigilance database.

9. When marketing authorisation holders do not use the Union pharmacovigilance database for signal management, they shall ensure that their record management system for adverse event reports contain all adverse event reports for which they are responsible. In particular, they shall ensure that adverse event reports concerning their veterinary medicinal products reported to the Union pharmacovigilance database from other sources are recorded in their own database.

([4]) https://www.ema.europa.eu/en/documents/scientific-guideline/vich-gl24-guideline-pharmacovigilance-veterinary-medicinal-products-management-adverse-event-reports_en.pdf

Article 18

Monitoring benefit-risk balance

1. Marketing authorisation holders shall continuously monitor the benefit-risk balance of their products in light of all available information from veterinarians, other healthcare professionals, the general public, adverse event reports by other marketing authorisation holders or competent authorities recorded in the Union pharmacovigilance database, and scientific literature.

2. Marketing authorisation holders shall continuously monitor the benefit-risk balance and take necessary risk minimisation measures to optimise the safe use of their veterinary medicinal products.

3. Marketing authorisation holders shall consider the potential impact of each adverse event on the benefit-risk balance of their products, unless there is no causal link between their products and the adverse event.

Article 19

Conclusion on the benefit-risk balance

1. Marketing authorisation holders shall annually record a conclusion on the benefit-risk balance for each of their products in the Union pharmacovigilance database and confirm that the signal management process has been conducted.

2. The outcome of the signal management process shall be included in the conclusion referred to in paragraph 1 if a new validated signal or signals related to medically important Veterinary Dictionary for Drug Regulatory Activities (VeDDRA) terms have been identified, even if no further action is considered necessary. The conclusion shall explain whether the benefit-risk balance is still considered as favourable and if any actions to improve the benefit-risk balance are deemed necessary.

3. When marketing authorisation holders identify a new risk or a change of the benefit-risk balance of one of their products, a summary of the analysis and a conclusion on the benefit-risk balance shall be recorded in the Union pharmacovigilance database. This shall be done in accordance with the timelines in Article 81(2) of Regulation (EU) 2019/6, notifying the competent authority or the Agency, as applicable.

Article 20

Communication

1. Marketing authorisation holders shall have an overarching communication plan that identifies the relevant stakeholders in the Union, including veterinarians, other healthcare professionals, customers and the general public. In cases of urgent safety concerns, it shall outline the approach to be taken to communicate in a timely manner concerns arising from pharmacovigilance data or in relation to other relevant pharmacovigilance information.

2. The communication plan shall include information on how marketing authorisation holders:

(a) identify the target audience;

(b) identify effective means for communication with the intended target audience;

(c) identify the specific objectives of the communication;

(d) define a timetable for the communication;

(e) ensure the relevance and clarity of the information for the intended target audience;

(f) identify and coordinate all stakeholders involved in the communication;

(g) give prior or simultaneous notification to the competent authority or the Agency, as applicable, of any public announcement on pharmacovigilance information, in accordance with Article 77(11) of Regulation (EU) 2019/6;

(h) measure the effectiveness of the communication.

3. Marketing authorisation holders shall use the data-processing network of the Union pharmacovigilance database for communication of alerts related to pharmacovigilance data.

CHAPTER 4

THE PHARMACOVIGILANCE SYSTEM MASTER FILE

Article 21

General requirements for the pharmacovigilance system master file

1. The information in the pharmacovigilance system master file required under Article 77(2) of Regulation (EU) 2019/6 shall be accurate and reflect the pharmacovigilance system in place.

2. The contractual arrangements between marketing authorisation holders and third parties concerning pharmacovigilance activities shall be clearly documented, detailed and up-to-date.

3. Marketing authorisation holders may, where appropriate, use separate pharmacovigilance systems for different categories of veterinary medicinal products. Each such system shall be described in a separate pharmacovigilance system master file.

Article 22

Content and structure of the pharmacovigilance system master file

1. The pharmacovigilance system master file shall consist of a main part describing the pharmacovigilance system, together with annexes containing detailed information.

2. The main part of the pharmacovigilance system master file shall contain the following Sections:

(a) Section A containing general information regarding the pharmacovigilance system master file:

  (i) pharmacovigilance system master file reference number;

  (ii) pharmacovigilance system master file location for the purpose of pharmacovigilance inspections in accordance with Article 126(4) of Regulation (EU) 2019/6;

(b) Section B containing information regarding the qualified person responsible for pharmacovigilance, assistant veterinary surgeon and associated back-up procedures:

  (i) information on the qualified person responsible for pharmacovigilance including name, contact details and a signed statement from the marketing authorisation holder and the qualified person confirming that the qualified person concerned has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6;

  (ii) documentation on the marketing authorisation holder arrangements concerning the assistant veterinary surgeon referred to in Article 3(2), if applicable, including the contact details;

  (iii) a description of back-up arrangements that apply in the absence of the qualified person responsible for pharmacovigilance or the veterinary surgeon, assisting the qualified person responsible for pharmacovigilance referred to in Article 2(6);

(c) Section C containing information on the marketing authorisation holder:

  (i) a detailed description of the organisational structure of the marketing authorisation holder, including a parent company or group of companies associated;

  (ii) the position of the qualified person responsible for pharmacovigilance within the organisation.

(d) Section D containing a description of the document management system referred to in Article 5, including the record management system for adverse event recording referred to in Article 10;

(e) Section E containing a description of the quality management system for pharmacovigilance activities, including all of the following:

(i) a description of the processes used for pharmacovigilance activities referred to in Article 4(3), (4), (5) and (6);

(ii) a description of the training management system in place referred to in Article 6(2);

(iii) a description of the system used for documenting or archiving information referred to in Article 5(2);

(iv) a description of the system for monitoring the performance of the pharmacovigilance system as referred to in Article 7;

(v) a description of the responsibilities for quality assurance auditing of the pharmacovigilance system as referred to in Article 8 including, where appropriate, auditing of subcontractors;

(vi) a list of audits associated with unresolved critical or major findings;

(vii) a description of the corrective and preventive action plan management and change management in place as referred to in Article 9;

(f) Section F containing a description of the contractual arrangements between marketing authorisation holders and third parties concerning pharmacovigilance activities, where applicable.

3. The pharmacovigilance system master file shall contain the following Annexes:

(a) Annex I: a logbook containing records of all changes to the main part of the pharmacovigilance system master file;

(b) Annex II: additional information regarding the qualified person responsible for pharmacovigilance, assistant veterinary surgeon, and associated back-up arrangements:

(i) curriculum vitae including information on qualifications and training of the qualified person responsible for pharmacovigilance as referred to in Article 3(1) and, if applicable, the assistant veterinary surgeon as referred to in Article 3(2);

(ii) a description of the tasks and responsibilities of the qualified person responsible for pharmacovigilance;

(iii) proof of registration with the pharmacovigilance database;

(iv) a list of the pharmacovigilance activities that have been delegated by the qualified person responsible for pharmacovigilance to third parties;

(c) Annex III: additional information on the marketing authorisation holder:

(i) a list of all veterinary medicinal products covered by the pharmacovigilance system master file, including the international non-proprietary name (INN) of the active substances, if applicable, the Member States in which the product is authorised or registered, the type of procedure for authorisation and the authorisation numbers in each Member State where the product is authorised;

(ii) a list of reference numbers for other pharmacovigilance system master files held by the same marketing authorisation holder, where applicable;

(iii) 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;

(iv) a list of the sites where pharmacovigilance activities listed in Article 4(3), (4), (5) and (6) are carried out;

(d) Annex IV: further details about the quality management system:

(i) a list of documents, policies, procedures and processes used for the pharmacovigilance activities referred to in Article 4(3), (4), (5) and (6);

(ii) a list of all scheduled and completed audits including outstanding critical and major findings.;

(iii) a list of performance indicators and how to use them, as referred to in Article 7, as applicable;

(iv) the information on training plans and records referred to in Article 6(2);

(v) the methodology to calculate the factor referred to in Article 14(2);

(vi) a list of risk management measures and the outcome of risk minimisation measures;

(e) Annex V: further information on contractual arrangements between marketing authorisation holders and third parties concerning pharmacovigilance activities:

(i) a list of the activities or services subcontracted by the marketing authorisation holder to third parties to fulfil pharmacovigilance obligations and information on who the activities or services are subcontracted to, including the name and address any subcontractors, where applicable;

(ii) 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 and the information on who the activities or services are subcontracted to, including the name and address of the subcontractor(s), where applicable;

(iii) a list of existing contracts and agreements with third parties, where applicable, including the products and territories concerned.

4. Where appropriate, information may be provided in the form of charts or flow diagrams.

Article 23

Summary

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

(a) the pharmacovigilance system master file reference number;

(b) the pharmacovigilance system master file location;

(c) name, contact details and place of operation of the qualified person responsible for pharmacovigilance;

(d) the signed statement referred to in Article 22(2)(b), point (i);

(e) the type of record management system used for adverse events reports including the name of the database, if applicable.

Article 24

Maintenance

1. Marketing authorisation holders shall keep the pharmacovigilance system master file up to date and revise it, where necessary, to take account of experience gained, and of technical and scientific progress.

2. Marketing authorisation holders shall ensure that the qualified person responsible for pharmacovigilance has permanent access to the pharmacovigilance system master file to fulfil the tasks referred to in Article 78 of Regulation (EU) 2019/6.

3. The pharmacovigilance system master file shall be subject to version control and indicate the date when it was last updated.

4. Marketing authorisation holders shall record in a logbook any alteration to the content of the main part of the pharmacovigilance system master file made within the last 5 years. Marketing authorisation holders shall indicate in the logbook the changed Section, the kind of change, the date, the person responsible and, where appropriate, the reason for the alteration.

5. Marketing authorisation holders shall, upon request, submit a copy of their logbook or another requested part of the pharmacovigilance system master file to the competent authorities or the Agency, as applicable, within 7 days.

6. Marketing authorisation holders shall notify the relevant competent authority or the Agency of any change in the information provided in the summary of the pharmacovigilance system master file by submitting a variation in accordance with Article 61 of Regulation (EU) 2019/6.

7. After the system as described in the pharmacovigilance system master file has been formally terminated, marketing authorisation holders shall keep an electronic version of it for 5 years.

Article 25

Location and availability

1. The pharmacovigilance system master file shall be located in the Union at the site where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site where the qualified person responsible for pharmacovigilance operates.

2. The pharmacovigilance system master file may be stored or made available in electronic form. The media used for storage or making available shall be searchable and shall remain readable over time.

3. When requested, a printed copy of the pharmacovigilance system master file arranged in accordance with Article 22(2) and (3), or parts thereof, shall be made available for audits and inspections. The printed copy or the requested part shall be complete and legible.

4. The pharmacovigilance system master file shall be permanently and immediately available for inspection at the site where it is kept. If the pharmacovigilance system master file is kept in electronic form, it is sufficient that the data stored in electronic form are directly available.

CHAPTER 5

CONTROLS AND INSPECTIONS BY COMPETENT AUTHORITIES

Article 26

Controls

1. Marketing authorisation holders shall be ready for controls in accordance with Article 123 of Regulation (EU) 2019/6 and shall also ensure the following are ready for those controls:

(a) their qualified person responsible for pharmacovigilance in accordance with Article 77(8) of Regulation (EU) 2019/6; and

(b) their representatives responsible for the reporting of adverse events in accordance with Article 14(1)(a) and (l) and Article 77(3) of Regulation (EU) 2019/6;

(c) any other natural or legal person carrying out pharmacovigilance activities in whole or in part, on behalf of or in conjunction with marketing authorisation holders.

2. Pharmacovigilance inspections carried out in accordance with Article 123(6) of Regulation (EU) 2019/6 may be performed as on-site or remote inspections.

Article 27

Pharmacovigilance inspections

1. Marketing authorisation holders shall be prepared for inspections of their pharmacovigilance system and the corresponding pharmacovigilance system master file in accordance with Article 123(6) and Article 126 of Regulation (EU) 2019/6 and shall ensure the same for any person mentioned in Article 26(1).

2. Marketing authorisation holders may be inspected on the site where the pharmacovigilance system master file is located or at any other site of those persons inspected in accordance with paragraph 1. With regard to a third party carrying out pharmacovigilance activities, the site to be inspected may be located within or outside the Union.

3. Marketing authorisation holders shall provide the necessary information requested by the competent authorities or the Agency in accordance with Article 79(6) of Regulation (EU) 2019/6 for on-site or remote inspections.

4. Pharmacovigilance inspections may be either routine inspections or targeted inspections; they may be product-specific or inspections of the general pharmacovigilance system. On the occasion of an inspection, marketing authorisation holders shall:

(a) present proof that they have personnel, systems and facilities in place to meet their pharmacovigilance obligations and that they are ready for inspection at any time;

(b) present proof in regard to their contractual arrangements, including a clear description of the roles and responsibilities of third parties to whom pharmacovigilance activities are subcontracted and provisions for their inspection and audit;

(c) demonstrate that the pharmacovigilance system is in compliance with legislation or relevant pharmacovigilance guidelines;

(d) provide information on the corrective and preventive action plan management and demonstrate the functionality and the implementation of any change management.

5. Marketing authorisation holders may be required by the competent authority or the Agency to communicate the corrective and preventive action plan in accordance with Article 9(2).

Article 28

Entry into force

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

It shall apply from 28 January 2022.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 2 August 2021.

For the Commission
The President
Ursula VON DER LEYEN