South African Health Products
Regulatory Authority
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GUIDELINE ON PHARMACOVIGILANCE SYSTEMS

This guideline is intended to provide guidance to the applicants/holders of Certificate of Registration (HCRs) on the pharmacovigilance system requirements. It is meant to facilitate compliance by applicants/HCRs with the regulatory authority on pharmacovigilance requirements. It represents the Authority's current thinking on the safety, efficacy, and quality of medicines. SAHPRA reserves the right to request any additional information to establish the safety, efficacy, and quality of a medicine in keeping with the knowledge current at the time of evaluation.

Document History

Final Version	Reason for Amendment	Effective Date
1	First issue	09 May 2022
2	- Content structured on the latest SAHPRA Guideline Template - The following sections are amended: o Section 3 moved to 6.1.3 o Section 7.3 and 7.4 for requirements and responsibilities of the holder of certificate of registration o Section 8 for Local Pharmacovigilance Officer o Section 9.1.8 for addition of requirements for summary PSMF o Section 9.4.10(b) and (c) moved to Section 9.5.8 and Section 9.4.10(a) moved to Section 9.1.7 o Section 9.5.6 and 9.5.8 for PSMF accessibility and submission	01 October 2023

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Contents

Glossary

Abbreviation/ Term	Meaning
Applicant	Anyone who has submitted any kind of application for medicine registration.
Auditing	An independent and objective activity designed to add value and improve an organisation's operations by helping an organisation to accomplish its objectives by using a systematic, disciplined approach to evaluate and improve the effectiveness of risk management, control and governance processes; and "audit" and "inspection" have corresponding meanings.
Authority	Means the South African Health Products Regulatory Authority established by section 2 of the Act.
Certificate of registration	A certificate of registration issued under section 15, 15A or 15B of the Act.
Computerised system	A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control.
Holder of Certificate of Registration (HCR)	A person or the company or legal entity in whose name the registration for a medicine (a registration certificate) has been granted and who is responsible for all aspects of a medicine including quality, safety and compliance with the conditions of registration. For the purpose of this guideline, this definition extends to the company or legal entity in whose name old medicine is marketed.
Individual Case Safety Report	A document in a specific format for the reporting of one or several suspected adverse reactions to a medicinal product that occur in a single patient at a specific point of time.
License Holder	A person or establishment issued with a Section 22C (1)(b) license to manufacture, import, export, wholesale and distribute medicines and scheduled substances.
Licensee	Refers to the license holder.
Local Pharmacovigilance Officer (LPVO)	A local pharmacovigilance officer (LPVO) is a contact person for the HCR's pharmacovigilance system at a national level whose responsibilities are the same as those of the QPPV. LPVO is applicable for multinational HCRs whose QPPV resides elsewhere.
Logbook	A logbook is used to record changes to the PSMF to enable keeping track of the history of changes (specifying the date and the nature of the change and description of the changes made to the contents of the master file).

Medicine	Any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in - • the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in humans; or • restoring, correcting or modifying any somatic or psychic or organic function in humans; includes any veterinary medicine.
Periodic Benefit-Risk Evaluation Report (PBRER)	An update of the world-wide marketing experience of a medicinal product at defined times with focus on formal evaluation of benefit in special population at defined times during post- registration period.
Periodic Safety Update Reports (PSURs)	A regular update of the world-wide safety experience of a medicinal product at defined times during post-registration period.
Pharmacovigilance	The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.
Qualified Person Responsible For Pharmacovigilance (QPPV)	A Qualified Person Responsible For Pharmacovigilance (QPPV) is an individual, on full-time employment by the HCR, who is responsible for overall pharmacovigilance for all medicines of the HCR. The QPPV is responsible for ensuring that the company (the HCR) meets its legal obligations for monitoring of the safety of the products marketed in South Africa, including the establishment and maintenance of the HCR's pharmacovigilance system, preparation pharmacovigilance reports, acts as a single contact point for the regulatory authority on a 24-hour basis and respond to any regulatory queries.
Risk Management Plan (RMP)	A systematic approach and set of Pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, and the assessment of effectiveness of those interventions and how these risks will be communicated to the Authority and the general population.

1. INTRODUCTION

This guideline contains guidance for the establishment and maintenance of quality assured pharmacovigilance systems for applicants/holders of certificate of registration (HCRs). A pharmacovigilance system consists of specific pharmacovigilance processes that are purposed to ensure good pharmacovigilance practice. It is the mandate of SAHPRA to ensure that evidence of existing and new adverse events, interactions, information with regard to post-marketing surveillance and vigilance is being monitored, analysed and acted upon in a functional pharmacovigilance system operational by the HCRs.

In accordance with Section 1 of the Medicines and Related Substances Act, Act 101 of 1965 as amended, 'vigilance', in relation to a medicine, medical device or IVD, means the continuous monitoring and evaluation of its safety, efficacy and performance profile and the management of any risk throughout its life-cycle.

Before a medicine is registered for use, evidence of its safety and efficacy is limited to the results from clinical trials, where patients are selected carefully and followed up very closely under controlled conditions. This means that at the time of a medicine registration, it has been tested in a relatively small number of selected patients for a limited length of time.

After registration, the medicine may be used in a large number of patients, for a long period of time and with other medicines. Rare and delayed side effects may emerge in such circumstances. It is therefore essential that the safety of all medicines is monitored throughout their use in healthcare practice.

A pharmacovigilance system is a system used by applicants/HCRs to fulfil their legal mandate and responsibilities in relation to pharmacovigilance and is designed to monitor the safety of all registered health products and detect any change to their risk-benefit balance. The pharmacovigilance legal requirements and good pharmacovigilance practice apply to all medicines registered in South Africa. The legislation has the primary aim to strengthen and rationalise pharmacovigilance and increase patient safety.

SAHPRA requires that applicants/HCRs operate a pharmacovigilance system for the fulfilment of their pharmacovigilance obligation.

1.1 Purpose

This guidance document is intended to facilitate compliance by the HCRs and to enhance consistency in the application of the regulatory requirements regarding good pharmacovigilance practices.

1.2 Scope

1.2.1 This guideline encompasses all aspects of a quality assured pharmacovigilance system including all

aspects of the risk management, such as the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of medicines for human use, the design and evaluation of post-authorisation safety studies and pharmacovigilance audits.

1.2.2 This guidance document outlines the expected pharmacovigilance system for the holders of certificate of registration to ensure that they:

a) have an adequate and effective pharmacovigilance system and its quality system for monitoring the medicines that are registered in order to protect public health;

b) maintain a pharmacovigilance system master file (PSMF);

c) have adequate, competent, appropriately qualified and trained staff to work on the pharmacovigilance system;

d) comply with the pharmacovigilance obligations as per the *Medicines and Related Substances Act 101 (Act 101 of 1965) as amended*, by ensuring that evidence of existing and new adverse events, interactions, information with regard to post-marketing surveillance and vigilance are monitored, analysed and acted upon.

2. LEGAL PROVISION

2.1 In accordance with Regulation 40 issued in terms of the Medicines and Related Substances Act, 101 of 1965, *as amended.*

(1) A person who has applied for registration of a medicine in terms of section 15 of the Act, a holder of a certificate of registration in respect of a medicine or Scheduled substance, or a holder of a licence in terms of section 22C (1) (b) must inform the Authority, in the manner and within the time frame as determined by the Authority. A holder of certificate of registration /applicant and licence holder must inform the Authority of any:

(a) new or existing quality, safety or effectiveness concerns related to any medicine or scheduled substance, including but not limited to adverse drug reactions; and

(b) risk management activities associated with paragraph (1)

(2) *A person who has applied for registration of a medicine in terms of section 15 of the Act, a holder of a certificate of registration in respect of a medicine or Scheduled substance, or a holder of a*

license in terms of section 22C (1) (b) must maintain or have access to records of the reports and case reports referred to in sub regulation (1) above.

3. REQUIREMENTS AND RESPONSIBILITIES OF THE HOLDER OF CERTIFICATE OF REGISTRATION

3.1 In order to comply with the regulatory pharmacovigilance requirements, the HCRs should:

a) establish and operate a pharmacovigilance system to ensure monitoring and supervision of their medicines registered/marketed in South Africa; including the following critical pharmacovigilance process:

- continuous safety profile monitoring and benefit-risk evaluation of registered medicines;
- establishing, assessing and implementing risk management systems and evaluating the effectiveness of risk minimisation;
- collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of individual case safety reports (ICSRs) from any source;
- signal management;
- scheduling, preparation (including data evaluation and quality control), submission and assessment of periodic safety update reports (PSURs)/ Periodic Benefit Risk Evaluation Report (PBRERs);
- meeting commitments and responding to requests from the Authority, including provision of correct and complete information;
- interaction between the pharmacovigilance and product quality defect systems;
- communication about safety concerns between HCRs and the Authority, in particular notifying changes to the risk-benefit balance of medicines;
- communicating information to patients and healthcare professionals about changes to the risk-benefit balance of products for the purpose of ensuring safe and effective use of medicines;
- keeping product information up-to-date with the current scientific knowledge, including the conclusions of the assessment and recommendations from the Authority;
- implementation of variations to marketing authorisations for safety reasons according to the urgency required.

b) develop, maintain and make available upon request a PSMF that describes the pharmacovigilance system for medicines registered/marketed in South Africa,

c) have an appropriately Qualified Person Responsible for Pharmacovigilance (QPPV) to be responsible for the establishment and maintenance of the pharmacovigilance system described in the PSMF,

d) establish and use a quality system that is adequate and effective for performing its pharmacovigilance activities,

e) develop and maintain product-specific risk management systems.

3.2 Overall, applicants/HCRs should ensure that structures and processes are in place to allow the QPPV to sufficiently fulfil their responsibilities. Applicants/HCRs should ensure that mechanisms are in place that allow the QPPV to access and receive all relevant information on, but not limited to:

a) emerging safety concerns and any other information relating to the benefit-risk evaluation of the medicines covered by the pharmacovigilance system,

b) ongoing or completed clinical trials and other studies that the applicant/HCR is aware of, and which may be relevant to the safety of the medicines;

c) information from sources other than from the specific applicant/HCR, e.g., from those with whom the applicant/HCR has contractual arrangements; and

d) the procedures relevant to pharmacovigilance which the applicant/HCR has in place at every level in order to ensure consistency and compliance across the organisation.

3.3 Applicants/HCRs are responsible for ensuring that the Responsible Pharmacist notify the SAHPRA via pvsubmissions@sahpra.org.za of the QPPV's appointment or any change in the QPPV's details within 30 calendar days.

3.4 In case of multinational HCRs, SAHPRA requires that the appointment of the LPVO be approved by the QPPV.

4. QUALIFIED PERSON RESPONSIBLE FOR PHARMACOVIGILANCE (QPPV)

4.1 Introduction

4.1.1 The applicant/HCR must have a permanently appointed Qualified Person Responsible for Pharmacovigilance (QPPV) for all of its medicines (including old medicines, biologicals and vaccines) in South Africa.

4.1.2 A Qualified Person Responsible for Pharmacovigilance (QPPV) is an individual, on full-time employment by the HCR, who is responsible for overall pharmacovigilance for all medicines of the HCR. The QPPV is responsible for ensuring that the company (the HCR) meets its legal obligations for

monitoring of the safety of the products marketed in South Africa, including the establishment and maintenance of the HCR's pharmacovigilance system, preparation of pharmacovigilance reports, acts as a single contact point for the regulatory authority on a 24-hour basis and responds to any regulatory queries.

4.1.3 For multinational HCRs, whose QPPV does not have a full oversight of the local pharmacovigilance system and/or resides elsewhere, the HCR should ensure that the QPPV nominate a local pharmacovigilance officer (LPVO). A LPVO is a contact person for the HCR's pharmacovigilance system at a national level whose responsibilities are the same as those of the QPPV.

4.1.4 LPVO is equated to a QPPV in terms of training, responsibilities, accountability and qualifications.

4.1.5 The QPPV should reside and operate in South Africa.

4.1.6 The QPPV:

a) is responsible for the establishment and maintenance of the local pharmacovigilance system.

b) should have access to the reports of suspected adverse reactions and the PSMF for South African registered products.

c) should be able to facilitate responses to pharmacovigilance queries raised by the Authority, including queries raised during pharmacovigilance inspections.

d) shall not be a consultant, but a full-time employee of the applicant/HCR.

4.1.7 Each pharmacovigilance system should have only one QPPV.

4.1.8 The applicant/HCR may outsource certain pharmacovigilance activities to a third-party organisation, excluding the role of the QPPV.

4.1 Qualifications of the QPPV

4.2.1 The person designated as the QPPV shall be a healthcare professional with Medicine, Pharmacy Nursing or any other healthcare professional or science degree. The Authority also accept a person who is not a healthcare professional, but with a relevant scientific discipline and at least two years minimum experience with specific job function in the area of pharmacovigilance for designation as the QPPV. This person should have access to a medically qualified person.

4.2.2 This person should have experience and training in all aspects of pharmacovigilance including the management of pharmacovigilance systems as well as expertise or access to expertise in relevant areas such as medicine, pharmaceutical sciences as well as epidemiology and biostatistics.

4.2.3 The QPPV shall receive formal training relevant to pharmacovigilance practice.

4.2 Responsibilities of the QPPV

4.3.1 The duties of the QPPV should be defined in a job description. The hierarchical relationship of the QPPV should be defined in an organisational chart together with those of other managerial and supervisory staff. Information relating to the QPPV should be included in the PSMF.

4.3.2 The responsibilities of the QPPV in relation to the pharmacovigilance system must include:

4.3.2.1 the establishment and maintenance of the HCR's pharmacovigilance system and therefore should have sufficient authority to influence the performance of the quality system and the pharmacovigilance activities and to promote, maintain and improve compliance with the legal requirements. Hence, the QPPV should have access to the PSMF and be in a position of authority to ensure and to verify that the information contained in the PSMF is an accurate and up-to-date reflection of the pharmacovigilance system under the QPPV's responsibility.

4.3.2.2 oversight over the functioning of the pharmacovigilance system in all relevant aspects, including its quality system (e.g., standard operating procedures, contractual arrangements, database operations, compliance data regarding quality, completeness and timeliness of expedited reporting and submission of periodic update reports, audit reports and training of personnel in relation to pharmacovigilance).

4.3.2.3 Act as a single point of contact for the Authority on all matters relating to pharmacovigilance and safety of marketed products including pharmacovigilance inspections.

4.3.3 The responsibilities of the QPPV in relation to the medicines covered by the pharmacovigilance system include:

4.3.3.1 Serve as a point of contact and in attendance during pharmacovigilance inspections.

4.3.3.2 Establish and maintain a system which ensures that information about all suspected adverse drug reactions/events which are reported to the personnel of the applicant/HCR, including to

medical representatives, is collected, collated, processed and evaluated and forwarded to the Authority in line with the timelines stipulated by the Authority.

4.3.3.3 Prepare and/or ensure that the following documents are submitted to the Authority;

i) Adverse drug reaction reports

ii) PSURs/PBRERs, when necessary

iii) Company-sponsored pre- and post-registration study reports

iv) Risk Management Plans (RMPs) and South Africa specific RMP as per the relevant guideline. The QPPV shall have sufficient authority over the content and implementation of risk management plans and risk minimisation measures.

v) Ongoing pharmacovigilance evaluation during the post- registration period.

4.3.3.4 Ensure that any request from the Authority for additional information deemed necessary for the evaluation of the risk-benefit ratio of a marketed product, is provided to the Authority promptly and fully.

4.3.3.5 Oversee the safety profiles of the company's marketed products and any emerging safety concerns. Have awareness of any conditions or obligations adopted as part of the registration certificate and other commitments relating to safety or the safe use of the products;

4.3.3.6 Be involved in the review and sign-off of local protocols of post-authorisation safety studies as agreed in the risk management plan,

4.3.3.7 Have awareness of post-authorisation safety studies requested by the Authority including the results of such studies;

4.3.3.8 Ensure conduct of pharmacovigilance and submission of all pharmacovigilance-related documents in accordance with the legal requirements;

4.3.3.9 Ensure the necessary quality, including the correctness and completeness, of pharmacovigilance data submitted to the Authority;

4.3.3.10 Ensure a full and prompt response to any request from the Authority for the provision of additional information necessary for the benefit-risk evaluation of medicines;

4.3.3.11 Provide any other information relevant to the benefit-risk evaluation of medicines to the Authority;

4.3.3.12 Provide input into the preparation of regulatory action in response to emerging safety concerns (e.g., variations, urgent safety restrictions notifications, and communication to patients and healthcare professionals);

4.3.3.13 Be involved in the clearance of any contractual agreements.

4.3 Back-up procedures

4.4.1 Back-up procedures in the case of absence of the QPPV should be in place and should be made available, together with the back-up person's contact details via the QPPV. It is not mandatory for the applicant/HCR to notify the Authority of the back-up QPPV.

4.4.2 The QPPV should ensure that the back-up person has all necessary information to fulfil the role.

4.4.3 The back-up person shall meet all the requirements of a QPPV. The back-up person shall receive training in all aspects of pharmacovigilance appropriate for his/her roles as the back-up QPPV.

4.4.4 In addition to the above, the back-up QPPV must reside in South Africa and have knowledge on applicable South African safety monitoring legislation and guidelines and international standards for pharmacovigilance and demonstrate (e.g., through qualifications and training) that he/she has knowledge of the key pharmacovigilance activities performed as part of the applicant/HCR's pharmacovigilance system and how to implement them.

5. PHARMACOVIGILANCE SYSTEM MASTER FILE (PSMF)

5.1 Introduction

5.1.1 The pharmacovigilance system master file is a detailed description of the pharmacovigilance system used by the applicant/HCR with respect to all medicines of which the applicant is the HCR. The PSMF is considered a key reference document for the company's personnel, on all aspects of day-to-day medicines' safety operations. It is therefore an important tool for providing oversight of the pharmacovigilance system and can be used by the QPPV to assist with medicines' oversight.

5.1.2 The PSMF, the standard operating procedures and trainings and the operational guidelines implementing the standard operating procedures, form a cornerstone of all pharmacovigilance activities. Consequently, the PSMF plays a pivotal role and requires expert knowledge to meet all the

regulator's requirements. Therefore, the PSMF requirement, is applicable to all applicants/HCRs, and for all medicines, (old or registered) in South Africa.

5.1.3 The PSMF creation, maintenance in a current and accessible state (accessible for audit and inspection purposes) and provision to the Authority can be outsourced to a third party, but the applicant/HCR retains ultimate responsibility for compliance with the legal requirements.

5.1.4 PSMF should be company specific and should form part of the company's Quality Management System (QMS).

5.1.5 The PSMF is not part of the medicine registration dossier and is maintained independently from the dossier. However, during the evaluation of a medicine registration application, the applicant may be requested to provide a copy of the PSMF for review, based on the risk profile of a health product.

5.1.6 Applicants are required, at the time of initial medicine registration application, to have in place a summary of the pharmacovigilance system that describes the system that will be in place and functioning at the time of approving a medicine registration and placing of the product on the market. The pharmacovigilance system in place at the current time should be described in a PSMF summary. Information about elements of the system to be implemented in future may be included, but these should be clearly described as planned rather than established or current.

5.1.7 Multinational HCRs with a local Affiliate/branch in South Africa, should have a PSMF that reflect the pharmacovigilance system on global level and the local level with "South Africa Annex" containing country specific content for the pharmacovigilance system on national level and global Annexes.

5.1.8 The PSMF summary should include:

a) Details (including CV, qualifications, pharmacovigilance training certification and course details and contact details) of the QPPV;

b) a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the pharmacovigilance tasks and responsibilities;

c) a reference to the location where the PSMF for the medicine(s) is kept.

5.1.9 It is accepted that, where no registration certificate (and master file) previously existed, there may be information that cannot initially be provided, for example, compliance information. Descriptions of what will be implemented should be provided instead

5.2 Objectives of a PSMF

5.2.1 The objectives of a PSMF are:

a) to describe the pharmacovigilance system and support/document its compliance with the requirements;

b) to contribute to the appropriate planning and conduct of audits by the applicant or HCR(s), the fulfilment of supervisory responsibilities of the QPPV, and of inspections or other verification of compliance by Authority;

c) to provide\ an overview of the pharmacovigilance system, which may be requested and assessed by Authority during medicines' registration application or post-registration.

5.3 Contents of a PSMF

5.3.1 The contents of a PSMF should reflect the global availability of safety information for medicines marketed in South Africa (presenting information on the pharmacovigilance system applied at global, regional and local levels). The contents of a PSMF should include:

5.3.1.1 Cover page

5.3.1.2 Details of the QPPV;

5.3.1.3 Details of the organisational structure of the applicant/HCR;

5.3.1.4 Details of all the sources of the relevant safety data;

5.3.1.5 Details of all electronic (computerised) systems and databases;

5.3.1.6 Details of all pharmacovigilance processes;

5.3.1.7 Details of the performance of all drug safety systems;

5.3.1.8 Details of all quality systems related to pharmacovigilance.

5.3.1.9 Annex to the PSMF.

5.3.1.1 PSMF Cover Page

5.3.1.1.1 The PSMF cover page should include, where applicable, a list of other PSMFs held by the same applicant/HCR. This list should include the PSMF number(s), and the name

of the applicant/HCR's QPPV responsible for the pharmacovigilance system used. If the pharmacovigilance system is managed by another party that is not an applicant/HCR, the name of the service provider should also be included.

5.3.1.2 PSMF section on QPPV

5.3.1.2.1 The information relating to the QPPV provided in the PSMF should include:

i) a description of the responsibilities guaranteeing that the qualified person has sufficient authority over the pharmacovigilance system in order to promote, maintain and improve compliance;

ii) a summary curriculum vitae with the key information on the role of the qualified person responsible for pharmacovigilance. The details provided in relation to the QPPV should also include the description of the QPPV qualifications, experience and registrations relevant to pharmacovigilance;

iii) contact details of the QPPV, which should include name, postal address, telephone, e-mail and represent the usual working address of the QPPV.

iv) details of back-up arrangements to apply in the absence of the QPPV

5.3.1.2.2 A list of tasks that have been delegated by the QPPV should also be included in the Annexes. This should outline the activities that are delegated and to whom and include the access to a medically qualified person if applicable.

5.3.1.3 PSMF section on the organisational structure of the applicant/HCR

5.3.1.3.1 A description of the organisational structure of the applicant/HCR relevant to the pharmacovigilance system must be provided (diagrams may be particularly useful). The description should provide a clear overview of the company(ies) involved, the main pharmacovigilance departments and the relationship(s) between organisations and operational units relevant to the fulfilment of pharmacovigilance obligations. This should include third parties as well.

5.3.1.3.2 Specifically, the PSMF should describe:

i) The organisational structure of the applicant/HCR(s), showing the position of the QPPV

in the organisation.

ii) The site(s) where the pharmacovigilance functions are undertaken covering individual case safety report collection, evaluation, safety database case entry, periodic safety update report production, signal detection and analysis, risk management plan management, pre- and post-authorisation study management, and management of safety variations to product particulars.

iii) Delegated activities

iv) The PSMF, where applicable, should contain a description of the activities and/or services subcontracted by the applicant/HCR relating to the fulfillment of pharmacovigilance obligations. This includes arrangements with other parties in any country, worldwide and if applicable, to the pharmacovigilance system applied to products registered in South Africa.

v) Links with other organisations, such as co-marketing agreements and contracting of pharmacovigilance activities should be outlined. A description of the location and nature of contracts and agreements relating to the fulfilment of pharmacovigilance obligations should be provided. Individual contractual agreements should be made available at the request of the Authority or during inspection and audit and the list provided in the Annexes.

5.3.1.4 PSMF section on the sources of safety data

5.3.1.4.1 The description of the main units for safety data collection should include all parties responsible (including on a global basis), for solicited and spontaneous case collection for products registered in South Africa.

5.3.1.4.2 This should include medical information sites as well as affiliate offices and may take the form of a list describing the country, nature of the activity and the product(s) (if the activity is product specific) and providing a contact point (address, telephone and e-mail) for the site. The list may be located in the Annexes of the PSMF. Information about third parties (license partners or local distribution/marketing arrangements) should also be included in the section describing contracts and agreements.

5.3.1.4.3 The description of the process for ICSRs, from collection to reporting to the Authority, should indicate the departments and/or third parties involved.

5.3.1.4.4 For the purposes of inspection and audit of the pharmacovigilance system, sources that include data arising from studies, registries, surveillance or support programmes sponsored by the applicant/HCR through which ICSRs are identified, should be reported. Applicants/HCRs should be able to produce and make available a list of such sources to support inspection, audit and QPPV oversight. The list should be comprehensive for products registered in South Africa, irrespective of indication, product presentation or route of administration.

5.3.1.5 PSMF section on computerised systems and databases

5.3.1.5.1 The location, functionality and operational responsibility for computerised systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose should be described in the PSMF.

5.3.1.5.2 Where multiple computerised systems/databases are used, the applicability of these to pharmacovigilance activities should be described in such a way that a clear overview of the extent of computerisation within the pharmacovigilance system can be understood.

5.3.1.5.3 The validation status of key aspects of computer system functionality should also be described. The change control, nature of testing, back-up procedures and electronic data repositories vital to pharmacovigilance compliance should be included in summary, and the nature of the documentation available described.

5.3.1.5.4 For paper-based systems (where an electronic system may only be used for expedited submission of ICSRs), the management of the data, and mechanisms used to assure the integrity and accessibility of the safety data, and in particular the collation of information about adverse drug reactions, should be described.

5.3.1.6 PSMF section on pharmacovigilance processes

5.3.1.6.1 An essential element of any pharmacovigilance system is that there are clear written procedures in place.

5.3.1.6.2 A description of the procedural documentation available (standard operating

procedures, manuals), the nature of the data held (e.g., the type of case data retained for ICSRs) and an indication of how records are held (e.g., safety database, paper file at site of receipt) should be provided in the PSMF.

5.3.1.6.3 A description of the process, data handling and records for the performance of pharmacovigilance activities, covering the following aspects should be included in the PSMF:

i) Continuous monitoring of product risk-benefit profile(s) applied and the result of evaluation and the decision-making process for taking appropriate measures; this should include signal generation, detection and evaluation. This may also include several written procedures and instructions concerning safety database outputs, interactions with clinical departments, etc;

ii) Risk management system(s) and monitoring of the outcome of risk minimisation measures; several departments may be involved in this area and interactions should be defined in written procedures or agreements;

iii) ICSR collection, collation, follow-up, assessment and reporting; the procedures applied to this area should clarify what are local and what are global activities;

iv) PSUR scheduling, production and submission, if applicable;

v) Communication of safety concerns to consumers, healthcare professionals and the Authorities;

vi) Implementation of safety variations to the Professional Information and Patient Information Leaflets; procedures should cover both internal and external communications.

5.3.1.6.4 For each process, the applicant/HCR should be able to provide evidence of a system that supports appropriate and timely decision making and action.

5.3.1.6.5 Description of interfaces with other functions should be in place. These include but are not limited to the roles and responsibilities of the QPPV, responding to the Authority's requests for information, literature searching, safety database change control, safety data exchange agreements, safety data archiving, pharmacovigilance auditing, quality

control and training.

5.3.1.6.6 There should be a list (which may be in the Annexes) that comprise the procedural document reference number, title, effective date and document type (for all standard operating procedures, work instructions, manuals etc.).

5.3.1.6.7 Procedures belonging to service providers and other third parties should be clearly identified.

5.3.1.7 PSMF section on pharmacovigilance system performance

5.3.1.7.1 The PSMF should contain evidence of the ongoing monitoring of performance of the pharmacovigilance system including compliance of the main outputs of pharmacovigilance. The PSMF should include a description of the monitoring methods applied and contain as a minimum:

i) An explanation of how the correct reporting of ICSRs is assessed. In the annex, figures/graphs should be provided to show the timeliness of reporting over the past year;

ii) A description of any metrics used to monitor the quality of submissions and performance of pharmacovigilance. This should include information provided by the Authority regarding the quality of ICSR reporting, PSURs or other submissions;

iii) An overview of the timeliness of PSUR reporting to the Authority;

iv) An overview of the methods used to ensure timeliness of safety variation submissions compared to internal and Authority deadlines, including the tracking of required safety variations that have been identified but not yet submitted;

v) Where applicable, an overview of adherence to risk management plan commitments, or other obligations or conditions of registration relevant to pharmacovigilance.

5.3.1.7.2 Targets for the performance of the pharmacovigilance system should be described and explained. A list of performance indicators must be provided in the Annex to the PSMF, alongside the results of (actual) performance measurements.

5.3.1.8 PSMF section on quality system

5.3.1.8.1 A description of the quality management system should be provided, in terms of the structure of the organisation and the application of quality to pharmacovigilance.

5.3.1.8.2 This should include:

i) Document and Record Control

a) A description of the archiving arrangements for electronic and/or hardcopy versions of the PSMF should be provided, as well as an overview of the procedures applied to other quality system and pharmacovigilance records and documents.

ii) Procedural documents

a) A general description of the types of documents used in pharmacovigilance (standards, operating procedures, work instructions etc.), the applicability of the various documents at global, regional or local level within the organisation, and the controls that are applied to their accessibility, implementation and maintenance.

b) Information about the documentation systems applied to relevant procedural documents under the control of third parties. A list of specific procedures and processes related to the pharmacovigilance activities and interfaces with other functions, with details of how the procedures can be accessed must be provided.

iii) Training

a) A description of the resource management for the performance of pharmacovigilance activities: the organisational chart showing the number of people (full time equivalents) involved in pharmacovigilance activities (may be provided in the section describing the organisational structure);

b) A description of the training provided by the organisation in relation to the personnel and site information should be provided;

c) A summary description of the training concept, including a reference to the location training files. Staff should be appropriately trained for performing pharmacovigilance related activities and this includes not only staff within pharmacovigilance departments but also any individual that may receive safety reports.

iv) Auditing

a) Information about quality assurance auditing of the pharmacovigilance system should be included in the PSMF.

b) A description of the approach used to plan audits of the pharmacovigilance system and the reporting mechanism and timelines should be provided, with a current list of the scheduled and completed audits concerning the pharmacovigilance system maintained in an annex. This list should describe the date(s) (of conduct and of report), scope and completion status of audits of service providers, specific pharmacovigilance activities or sites undertaking pharmacovigilance and their operational interfaces relevant to the fulfilment of the obligations and cover a rolling 5-year period.

c) The PSMF should also contain a note associated with any audit where significant findings are raised. This means that the presence of findings whether major or critical findings must be indicated.

d) The audit report must be documented within the quality system; in the PSMF it is sufficient to provide a brief description of the corrective and/or preventative action(s) associated with the significant finding, the date it was identified and the anticipated resolution date(s), with cross reference to the audit report and the documented corrective and preventative action plan(s).

e) In cases where corrective and preventative action plan(s) have not yet been agreed for a particular audit or finding, the PSMF should include the note required and stating that “corrective and preventative action plan(s) are to be agreed”.

f) In the annex, on the list of audits conducted, those associated with unresolved notes in the PSMF, should be identified. The note and associated corrective and preventative action(s), should be documented in the PSMF until the corrective and/or preventative action(s) have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently verified.

g) The addition, amendment or removal of the notes should therefore be recorded in the logbook.

h) As a means of managing the pharmacovigilance system, and providing a basis for audit or inspection, the PSMF should also describe the process for recording, managing and resolving deviations from the quality system. The master file should

also document deviations from pharmacovigilance procedures, their impact and management until resolved. This may be documented in the form of a list referencing a deviation report, and its date and procedure concerned.

5.3.1.9 Annex to the PSMF

5.3.1.9.1 An annex to the PSMF shall contain the following documents which shall be presented with the following headings and, if hardcopy, in the order outlined below:

NB: Where there is no content for an Annex, it should simply be described as 'unused' in the indexing so the recipients of the PSMF are assured that missing content is intended. In these cases, the Annexes that are provided should still be named according to the format described below **without** reordering.

a) Annex A - The QPPV

- The list of tasks that have been delegated by the QPPV, or the applicable procedural document.
- The curriculum vitae of the QPPV and associated documents.
- Contact details supplementary to those contained, if appropriate.

b) Annex B - The Organisational Structure of the applicant/HCR

- The lists of contracts and agreements covering delegated activities including the medicines and territory(ies) concerned.

c) Annex C - Sources of safety data

- Lists associated with the description of sources of safety data e.g., affiliates and third-party contacts.

d) Annex D - Computerised systems and Databases

e) Annex E - Pharmacovigilance Process, and written procedures

- Lists of procedural documents.

f) Annex F - Pharmacovigilance System Performance

- Lists of performance indicators.
- Current results of performance assessment in relation to the indicators.

g) Annex G - Quality System

- Audit schedules.
- List of audits conducted and completed for a period of five years.

h) Annex H - Products

- List(s) of products covered by the pharmacovigilance system including the name of the medicine, the international non-proprietary name of the active substance(s); the registration number(s); the type of conditions of registration.
- Any notes concerning the applicant/HCR per product
- The following should be considered for these lists:

  i) The list should be organised per active substance and, where applicable, should indicate the type of product specific safety monitoring requirements exist (for example, risk minimisation measures contained in the risk management plan or laid down as conditions of registration, or/and a PSUR periodicity). The monitoring information may be provided as a secondary list.

  ii) For registration certificates that are included in a different pharmacovigilance system (for example, because the applicant/HCR has more than one pharmacovigilance system or third-party agreements exist to delegate the system), reference to the additional PSMF(s) should also be provided as a separate list in the Annexes, such that, for an applicant/HCR, the entire product portfolio can be related to the set of PSMFs.

i) Annex I - Document and Record Control

- Logbook
- Documentation of history of changes for Annex contents, indexed according to the Annexes A-H and their content if not provided within the relevant annex itself.

- Documented changes should include at least the date, person responsible for the change and the nature of the change.

5.4 PSMF presentation, format and layout

5.4.1 The PSMF should include documents that describe the pharmacovigilance system.

5.4.2 The PSMF should be written in English, indexed in a consistent manner, and allow easy navigation to the contents.

5.4.3 The information should be succinct, accurate and reflect the current system in place, which means that whatever format is used, it must be possible to keep the information up-to-date and, when necessary, to revise, taking into account experience gained, technical and scientific progress and amendments to the legislative requirements.

5.4.4 The PSMF should be legible, complete, provided in a manner that ensures all documentation is accessible and allow full traceability of changes. Therefore, it may be appropriate to restrict access to the PSMF in order to ensure appropriate control over the content and to assign specific responsibilities for the management of PSMF in terms of change control and archiving.

5.4.5 The primary topic sections should contain information that is fundamental to the description of the pharmacovigilance system. Detailed information is required to fully describe the system, and, since this may change frequently, it should be referred to and contained in the Annexes.

5.4.6 The PSMF should reference existing SOPs in the applicant/HCR's QMS, such as change control and computer system validation etc.

5.4.7 Embedded documents are discouraged.

5.4.8 The use of electronic book-marking and searchable text is recommended. Documents such as copies of signed statements or agreements should be included as appendices and described in the index.

5.4.9 The PSMF may be in electronic form on condition that a clearly arranged printed copy can be made available to the Authority if requested.

5.5 Accessibility and submission of the PSMF

5.5.1 The PSMF shall be located either at the site where the main pharmacovigilance activities are performed or at the site where the QPPV operates, irrespective of the format (paper-based or electronic format file). Based on this, the PSMF shall be located in South Africa. An

exception is where the main activities take place outside South Africa (e.g., multinational HCRs/applicants); the location should then default to the site where the QPPV operates or where the main pharmacovigilance activities are performed provided that:

a) the PSMF is made available to the Authority at any time; and

b) the local office/ affiliate of the HCR/applicant has detailed description on the pharmacovigilance system/ activities on the local level.

5.5.2 The PSMF should be kept up to date and be continuously available and accessible to the QPPV and for inspection, irrespective of whether the inspection has been notified in advance or is unannounced.

5.5.3 The PSMF is not routinely required by the Authority during the evaluation/assessment of new registration certificate applications (i.e., pre-registration), but may be requested on an ad hoc basis, particularly if:

a) a new pharmacovigilance system is being implemented;

b) product-specific safety concerns have been identified;

c) issues with compliance with pharmacovigilance requirements have been identified.

5.5.4 Although provision of the document within 14 calendar days of request by the Authority is required, the applicants/HCRs should be aware that immediate access to the PSMF may also be required by the Authority.

5.5.5 The applicant/HCR should submit the PSMF electronically to the Authority, within 14 calendar days after receipt of the request from the Authority.

5.5.6 The PSMF should be submitted in a readable electronic format.

5.5.7 In the situation where a common pharmacovigilance system is used by applicants/HCRs, each applicant/HCR should have their own PSMF. The PSMF should be accessible and be made available to the Authority within 14 calendar days upon request.

5.5.8 Consideration for the Multinational Pharmaceutical Companies

a) When the company is to submit a PSMF; both the EU/global PSMF of the Multinational

HCR and the PSMF local annex should be submitted to the Authority.

This local annex should include the following:

i) The contact details, qualification, CV and job description of the QPPV

ii) The lists of contracts and agreements relevant to pharmacovigilance on national level.

iii) List of Pharmacovigilance- relevant SOPs used on national level.

iv) List of Pharmacovigilance performance indicators and their current results on national level over the past year.

v) List of pharmacovigilance audits and their findings for company office on national level over the past 5 years.

vi) List(s) of products registered/ under registration in South Africa covered by the pharmacovigilance system, indicating which of them have additional risk minimisation measures and/ or additional pharmacovigilance activities.

b) Multinational HCRs who have no operating office/branch in South Africa but are represented (in South Africa) through their agent/ importer/ distributer should have and maintain a PSMF (according to the PSMF content highlighted in this guideline) providing description of its local pharmacovigilance system in integration with the HCR pharmacovigilance system and according to the Safety Data Exchange Agreement (SDEA) in place between both parties. the PSMF should be accessible to the Authority as stipulated in this guideline.

6. PHARMACOVIGILANCE QUALITY SYSTEM

6.1 Introduction

6.1.1 The quality of a pharmacovigilance system can be defined as all the characteristics of the system that are considered to produce outcomes relevant to the objectives of pharmacovigilance. In general terms, quality is a matter of degree and can be measured. Measuring if the required degree of quality has been achieved necessitates pre-defined quality requirements. Quality requirements are those characteristics of a system that are likely to produce the desired outcome, or quality objectives.

6.1.2 A quality system is part of the pharmacovigilance system and consists of its own structures and processes. It covers organisational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system as well as appropriate resource management, compliance management and record management.

6.1.3 The overall quality objectives of a pharmacovigilance system are:

a) To minimise/mitigate/reduce harm from adverse reactions in humans arising from the use of registered medicines within or outside the terms of registration or from occupational exposure.

b) To promote the safe and effective use of medicines, through providing timely information about the safety of medicines to patients, healthcare professionals and the public.

c) To implement measures for continuously supervising the quality, safety and efficacy of registered medicines to ensure that their benefits outweigh their risks.

d) To provide independent, science-based recommendations on the quality, safety and efficacy of medicines, and on more general issues relevant to the promotion and protection of public health that involve medicines.

e) To publish impartial and comprehensive information about medicines and their use.

f) To comply with the legal requirements for pharmacovigilance tasks and responsibilities.

g) To contribute to the protection of patients and public health.

6.1.4 The pharmacovigilance quality system should be based on all of the following activities:

a) Quality planning - establishing structures and planning integrated 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 being carried out; and

d) Quality improvements - correcting and improving the structures and processes where necessary.

6.1.5 Applicants /HCRs should establish and maintain a quality assured pharmacovigilance system for its products.

6.1.6 Pharmacovigilance quality system is used by applicants/HCRs to fulfil the tasks and responsibilities of monitoring the safety of registered products and detection of any change to their risk-benefit balance.

6.2 Requirements for compliance management by applicant/HCR in relation to pharmacovigilance quality system

6.2.1 The pharmacovigilance quality system should have procedures and processes in place to ensure:

a) Continuous monitoring of pharmacovigilance data, the examination of options for risk minimisation and prevention and appropriate measures are taken by an applicant/HCR.

b) Scientific evaluation of all information on the risks of health products as regards patients' or public health, in particular as regards adverse reactions in human beings arising from use of the product within or outside the terms of its registration terms or associated with occupational exposure.

c) Submission of accurate and verifiable data on serious and non-serious adverse reactions to the Authority within the legally required timelines as stipulated in the 'SAHPGL-CEM-PV-04_Post-Marketing reporting of ADR to Human Medicines in South Africa' guidelines.

d) Quality, integrity and completeness of the information submitted on the risks of medicines, including processes to avoid duplicate submissions and to validate signals;

e) Effective communication by an applicant/HCR with the Authority, including communication on new or changed risks, the PSMF, risk management systems, risk minimisation measures, periodic safety update reports, corrective and preventive actions and post-authorisation safety studies;

f) Update of product information by an applicant/HCR in light of scientific knowledge;

g) Appropriate communication of relevant safety information to healthcare professionals and patients;

h) The retention of minimum elements of the PSMF as long as the system described in the PSMF exists and for at least further 5 years after it has been formally terminated by an applicant/HCR;

i) The retention of pharmacovigilance data and documents relating to individual registered health products as long as the registration certificate exists and for at least further 10 years after the registration certificate has ceased to exist;

6.3 Responsibilities for the quality system within an organisation

6.3.1 A sufficient number of competent and appropriately qualified and trained personnel should be available for the performance of pharmacovigilance activities. For the purpose of a systematic approach towards quality, the managerial staff of an applicant/HCR should be responsible for:

a) ensuring that the organisation documents the quality system;

b) ensuring that the documents describing the quality system are subject to document control in relation to their creation, revision, approval and implementation;

c) ensuring that adequate resources are available and that training is provided;

d) ensuring that suitable and sufficient premises, facilities and equipment are available;

e) ensuring adequate compliance management;

f) ensuring adequate record management;

g) reviewing the pharmacovigilance system including its quality system at regular intervals in risk-based manner to verify its effectiveness and introducing corrective and preventive measures where necessary;

h) ensuring that mechanisms exist for timely and effective communication, including escalation processes of safety concerns relating to health products within an organisation;

i) identifying and investigating concerns arising within an organisation regarding suspected

non-adherence to the requirements of the quality and pharmacovigilance systems and taking corrective, preventive and escalation action as necessary; and ensuring that audits are performed.

6.4 Training of personnel for Pharmacovigilance

6.4.1 Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes by applicant/HCR is intrinsically linked to the availability of a sufficient number of competent and appropriately qualified and trained personnel. All personnel involved in the performance of pharmacovigilance activities should receive continued training related to the roles and responsibilities of the personnel.

6.4.2 The training plans and records for documenting, maintaining and developing the competencies of personnel should be kept. Training plans should be based on training needs assessment and should be subject to monitoring.

6.4.3 The training should support continuous improvement of relevant skills, the application of scientific progress and professional development and ensure that staff members have the appropriate qualifications, understanding of relevant pharmacovigilance requirements as well as experience for the assigned tasks and responsibilities. All staff members of the applicant/HCR should receive and be able to seek information about what to do if they become aware of a safety concern. There should be a process in place within the applicant/HCR to check that training results in the appropriate levels of understanding and conduct of pharmacovigilance activities for the assigned tasks and responsibilities, or to identify unmet training needs, in line with professional development plans agreed for the applicant/HCR as well as the individual staff members.

6.4.4 Adequate training should also be considered by the applicant/HCR for those staff members to whom no specific pharmacovigilance tasks and responsibilities have been assigned but whose activities may have an impact on the pharmacovigilance system or the conduct of pharmacovigilance. Such activities include but are not limited to those related to clinical trials, technical product complaints, medical information, terminologies, sales and marketing, regulatory affairs, quality assurance, legal affairs and audits. Appropriate instructions on the processes to be used in case of urgency, including business continuity, should be provided by the applicant/HCR to their personnel.

6.5 Management and Reporting of Safety data

6.5.1 Applicants/HCRs should implement a procedure to ensure that the QPPV is able to obtain information from the adverse reaction database (or other systems to collate adverse reaction reports), to respond to urgent requests for information from the Authority, at any time.

6.5.2 If this procedure requires the involvement of other personnel, for example database specialists, then this should be taken into account in the arrangements made by applicants/HCRs for supporting the QPPV (including outside of normal working hours).

6.5.3 Specifically for the adverse reaction database, if applicable, the QPPV should be aware of the validation status of the database, including any failures that occurred during validation and the corrective actions that have been taken to address the failures. The QPPV should also be informed of significant changes that are made to the database (e.g., changes that could have an impact on pharmacovigilance activities).

6.6 Record management system

6.6.1 A record management system should be put in place for all documents used for pharmacovigilance activities, ensuring their retrievability as well as traceability of the measures taken to investigate safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process.

6.6.2 The record management system should support:

a) the management of the quality of pharmacovigilance data, including their completeness, accuracy and integrity.

b) timely access to all records;

c) effective internal and external communication; and

d) the retention of documents relating to the pharmacovigilance systems and the conduct of pharmacovigilance for individual health products, in accordance with the applicable retention periods.

6.6.3 In addition, applicants/HCRs should establish mechanisms enabling the traceability and follow-up of adverse reaction reports.

6.6.4 In this context, it should be ensured that the fundamental right to personal data protection is fully and effectively guaranteed in all pharmacovigilance activities in conformity with legal provisions applicable. The purpose of safeguarding public health constitutes a substantial public interest and consequently the processing of personal data should be justified if identifiable personal data are processed only where necessary and only where the parties involved assess this necessity at every stage of the pharmacovigilance process.

6.6.5 As part of a record management system, specific measures should therefore, be taken at each stage in the storage and processing of pharmacovigilance data to ensure data security and confidentiality. This should involve strict limitation of access to documents and to databases to authorised personnel respecting the medical and administrative confidentiality of the data.

6.6.6 There should be appropriate structures and processes in place to ensure that pharmacovigilance data and records are protected from destruction during the applicable record retention period.

6.6.7 The record management system should be described in a record management policy.

6.7 Documentation of the pharmacovigilance quality system

6.7.1 All elements, requirements and provisions adopted for the PV quality system should be documented in a systematic and orderly manner in the form of written policies and procedures, such as PV quality plans, quality manuals and quality records.

a) A PV quality plan documents the setting of quality objectives and sets out the processes to be implemented to achieve them. A procedure is a specified way to carry out a process and may take the format of a standard operating procedure and other work instruction or PV quality manual.

b) A PV quality manual documents the scope of the PV quality system, the processes of the PV quality system and the interaction between the two.

c) A PV quality record is a document stating results achieved or providing evidence of activities performed.

6.7.2 In order to have a systematic approach, applicants/HCRs should define the following in advance:

a) PV Quality objectives specific to their organisations in accordance with the overall quality objective and the structure- and process-specific quality objectives in accordance with each chapter of good pharmacovigilance practice; and

b) Methods for monitoring the effectiveness of the pharmacovigilance system.

6.7.3 It is recommended that the documentation of a pharmacovigilance quality system includes:

a) Documents on organisational structures and assignments of tasks to all personnel and authorities directly involved in pharmacovigilance tasks;

b) Training plans and records; Training plans and records should be kept and made available for audit and inspection;

c) Instructions for the compliance management processes;

d) Appropriate instructions on the processes to be used in case of urgency, including business continuity;

e) Performance indicators where they are used to continuously monitor the good performance of pharmacovigilance activities;

f) Reports of quality audits and follow-up audits, including their dates and results.

g) The methods of monitoring the efficient operation of the quality system and, in particular, its ability to fulfil the quality objectives;

h) A record management policy;

i) Records created as a result of pharmacovigilance processes which demonstrate that key steps for the defined procedures have been taken;

j) Records and reports relating to the facilities and equipment including functionality checks, qualification and validation activities which demonstrate that all steps required by the applicable requirements, protocols and procedures have been taken;

k) Records to demonstrate that deficiencies and deviations from the established quality system are monitored, that corrective and preventive actions have been taken, that solutions have been

applied to deviations or deficiencies and that the effectiveness of the actions taken has been verified.

6.8 Additional pharmacovigilance quality system documentation by applicants/HCRs

6.8.1 In addition to the PV quality system documentation, an applicant/HCR should document:

a) their human resource management in the PSMF;

b) job descriptions defining the duties of the managerial and supervisory staff;

c) an organisational chart defining the hierarchical relationships of managerial and supervisory staff;

d) instructions on critical processes in the PSMF; and

e) their record management system in the PSMF.

6.8.2 Pharmacovigilance Quality management system requirements should be documented in the PSMF.

6.9 Facilities and equipment for Pharmacovigilance

6.9.1 Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes is intrinsically linked with appropriate infrastructure to support the processes.

6.9.2 Infrastructure includes office space, information technology (IT) systems and storage space (electronic). Infrastructure should be located, designed, constructed, adapted and maintained to suit their intended purpose in line with the quality objectives for pharmacovigilance and should be sustainable.

6.9.3 Infrastructures that are critical for the conduct of pharmacovigilance should be subject to appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose. There should be processes in place to keep awareness of the valid terminologies in their valid versions and to keep the IT systems up-to-date accordingly.

7. BUSINESS CONTINUITY PLANS

7.1 Business continuity plans should be established in a risk-based manner and should include:

a) provisions for events that could severely impact on the organisation's staff and infrastructure in general or on the structures and processes for pharmacovigilance in particular; and

b) back-up systems for urgent exchange of information within an organisation, amongst organisations sharing pharmacovigilance tasks as well as between applicants/HCRs and Authorities.

8. MONITORING OF THE PERFORMANCE AND EFFECTIVENESS OF THE PHARMACOVIGILANCE SYSTEM AND ITS QUALITY SYSTEM

7.2 Processes to monitor the pharmacovigilance performance should include:

a) reviews at regular intervals of the systems by those responsible for management;

b) audits;

c) compliance monitoring using performance indicators;

d) inspections;

e) evaluating the effectiveness of actions taken with medicines for the purpose of minimising risks and supporting their safe and effective use in patients.

9. SUBCONTRACTING OF THE PHARMACOVIGILANCE TASKS

9.1 Applicants/HCRs may subcontract certain activities of the pharmacovigilance system to third-party organisations with appropriate oversight and interface, excluding the role of the QPPV. **The applicant/HCR shall nevertheless retain full responsibility for**:

a) the completeness and accuracy of the PSMF.

b) the fulfilment of all pharmacovigilance tasks and responsibilities and the quality and integrity of the pharmacovigilance system.

c) ensuring that an effective quality system is applied in relation to the subcontracted tasks.

9.2 The subcontracted organisation may be subject to inspection at the discretion of the Authority.

9.3 When subcontracting tasks to another organisation, the applicant/HCR shall draw up subcontracts with the aim of enabling compliance with the legal requirements by each party involved. A description of the subcontracted activities and/or services shall be included in the PSMF and a list of the subcontracts shall be included in an annex to the PSMF, specifying the product(s) and territory(ies) concerned. These contracts should:

a) be up-to-date, include sufficiently detailed descriptions of the delegated tasks, the responsibilities of each party, the related interactions and data exchange, together with, for example, agreed definitions, tools, assignments, timelines and regulatory reporting responsibilities.

b) contain clear information on the practical management of pharmacovigilance as well as related processes, including those for the maintenance of pharmacovigilance databases.

c) indicate which processes are in place for checking whether the agreed arrangements are being adhered to on an ongoing basis. In this respect, regular risk-based audits of the other organisation by the applicant/ HCR.

10. REFERENCES

10.1 The following related documents are referenced: European Medicines Agency: EMA/816573/2011 Rev 2 - Guideline on good pharmacovigilance practices (GVP) - Module II – Pharmacovigilance system master file (Rev 2) 2017, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-ii-pharmacovigilance-system-master-file-rev-2_en.pdf, September 2021.

10.2 European Medicines Agency: EMA/541760/2011- Guideline on good pharmacovigilance practices (GVP) Module I – Pharmacovigilance systems and their quality systems 2012, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-i-pharmacovigilance-systems-their-quality-systems_en.pdf, September 2021.

10.3 TFDA, (2018). National Guidelines for Monitoring Medicines Safety, 2018, Tanzania Food and Drugs Authority, Dar-es-Salaam, Tanzania., Third edition. Doc (tmda.go.tz), September 2021.

11. VALIDITY

This guideline is valid for a period of 5 years from the effective date of revision. It will be reviewed on this timeframe or as and when required.