South African Health Products
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Pharmacovigilance Inspections for Human Medicinal Products

This document has been prepared to serve as a guideline to those involved in the conduct of Pharmacovigilance inspections. It is meant to facilitate compliance with Good Pharmacovigilance Practice relating to the conduct and monitoring of Pharmacovigilance inspections. It is not intended as an exclusive approach.

Document History

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2		

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1. ABBREVIATIONS AND ACRONYMS

GLP	Good laboratory practice
GDP	Good distribution practice
GMP	Good manufacturing practice
HCR	Holders of certificate of registration
ICSR	Individual case safety reports
PSUR	Periodic safety update report
PSMF	Pharmacovigilance system master file
PASS	Post-authorisation safety studies
RMP	Risk Management Plan
CAPA	Corrective and Preventive Action
CT	Clinical Trial
CV	Curriculum vitae
GCP	Good Clinical Practice
HCR	Holder of Certificate of Registration
PAES	Post-Authorisation Efficacy Study
PBRER	Periodic Benefit Risk Evaluation Report
PI	Professional Information
PIL	Patient Information Leaflet
PV	Pharmacovigilance
PVIO	Pharmacovigilance Inspection Overview
QC	Quality Control
SAHPRA	South African Health Products Regulatory Authority
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction

2. DEFINITIONS AND DESCRIPTIONS

2.1 Applicant

Anyone who has submitted any kind of application;

2.2 Authority

Means the South African Health Products Regulatory Authority established by section 2 of the Act;

2.3 Certificate of registration

A certificate of registration issued under section 15, 15A or 15B of the Act.

2.4 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;

2.5 Holder of Certificate of Registration (HCR)

A person or the company or legal entity in whose name the registration for a product (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.

2.6 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.

2.7 Licence Holder

A person or establishment issued with a Section 22C (1)(b) licence to manufacture, import, export, wholesale and distribute medicines and scheduled substances.

2.8 Licensee

Refers to a licence holder.

2.9 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.

2.10 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.

2.11 Pharmacovigilance

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

2.12 Qualified Person Responsible For Pharmacovigilance (QPPV)

An individual named by the applicant/HCR and approved by the Authority as the person responsible for ensuring that the company (the HCR) meets its legal obligations for monitoring of the safety of the products marketed in South Africa.

2.13 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 risk will be communicated to the Authority and the general population.

3. INTRODUCTION

3.1 This guideline pertains to the planning, conducting, reporting and following-up of Pharmacovigilance inspections in South Africa. This guideline is designed to facilitate compliance by the applicants/HCRs and to enhance consistency in the application of the regulatory requirements regarding good pharmacovigilance practices. Veterinary medicinal products are outside the scope of the guideline.

3.2 South African Health Products Regulatory Authority (SAHPRA) shall conduct pharmacovigilance inspections of applicants/HCRs or any licence holder employed to fulfil the applicant/HCR's pharmacovigilance requirements to ensure compliance with regulatory pharmacovigilance obligations. Inspectors appointed by SAHPRA are empowered to inspect the premises, records, documents and pharmacovigilance system master file (PSMF) of the applicant/HCR or any firm or contractor employed by the applicant/HCR to perform the pharmacovigilance activities on their behalf. Applicants/HCRs are required to provide, on request, the PSMF to inform inspection conduct.

3.3 For the purpose of this guideline, "SAHPRA" refers to the South African Health Products Regulatory Authority, hereafter referred to as the Authority. The terms "holder of certificate of registration" and "applicant" are used interchangeably.

4. PURPOSE

4.1 The purpose of this guideline is to provide guidance on areas of inspection for applicants/HCRs and their contractors, to ensure that they:

i) have an adequate and effective quality system for monitoring the medicines in order to protect public health;
ii) maintain a pharmacovigilance system master file;
iii) have adequate, competent, appropriately qualified and trained staff to work on the pharmacovigilance system;
ιϖ) comply with the pharmacovigilance obligations as per the *Medicines and Related Substance Act (Act 101 of 1965) as amended.*

5. OBJECTIVES

5.1 The objectives of pharmacovigilance inspections are:

i) to ensure that applicants/HCRs have personnel, systems and facilities in place to meet their pharmacovigilance obligations;
ii) to improve pharmacovigilance system established by applicants/HCRs;
iii) to identify, record and address non-compliance which may pose a risk to public health;
iv) to use the inspection results as a basis for enforcement action, where considered necessary.

6. INSPECTIONS TYPES

6.1 Introduction

6.1.1 It is anticipated that the majority of inspections will be announced i.e., notified in 45 days advance to the inspected party, to ensure the availability of relevant individuals for the inspection. However, on certain occasions, it may be appropriate to conduct unannounced inspections or to announce an inspection at short notice (e.g., when the announcement could compromise the objectives of the

inspection or when the inspection is conducted in a short timeframe due to urgent safety reasons).

6.1.2 Pharmacovigilance inspections can either be system or product related. System-related inspections are designed to review the procedures, systems, personnel, and facilities in place and determine their compliance with regulatory pharmacovigilance obligations. Product specific examples may be used to demonstrate the operation of the pharmacovigilance system. Product-related inspections are primarily focused on product-related pharmacovigilance issues, including product-specific activities and documentation, rather than a general system review. Some aspects of the general system may still be examined as part of a product-related inspection.

6.2 Routine Pharmacovigilance Inspections

6.2.1 Routine pharmacovigilance inspections are inspections scheduled in advance as part of inspection programmes. There is no specific trigger to initiate these inspections, although a risk-based approach to optimize oversight activities should be implemented. These inspections are usually system inspections but one or more specific products may be selected as examples to verify the implementation of the system and to provide practical evidence of its functioning and compliance.

6.2.2 Routine pharmacovigilance inspections should examine compliance with SAHPRA's legislation and guidance, and the scope of such inspections should include the following elements, as appropriate:

6.2.2.1 Individual case safety reports (ICSRs):

i) collecting, receiving and exchanging reports from all types of sources, sites and departments within the pharmacovigilance system, including from those companies employed to fulfil applicant/HCR's pharmacovigilance obligations and departments other than drug safety;
ii) assessment, including mechanisms for obtaining and recording reporter assessments, company application of event terms, seriousness, expectedness and causality.
iii) follow-up and outcome recording, for example final outcome of cases of exposure in pregnancy and medical confirmation of consumer reported events;
iv) reporting according to the requirements for various types of reported ICSRs, including onward reporting to the regulatory pharmacovigilance unit and timeliness of such reporting;
v) record keeping and archiving for ICSRs;

6.2.2.2 Periodic safety update reports (PSURs), (as applicable):

i) completeness and accuracy of the data included, appropriateness of decisions concerning data that are not included;
ii) addressing safety topics, providing relevant analyses and actions;
iii) formatting according to requirements;
iv) timeliness of submissions;

6.2.2.3 Ongoing safety evaluation;

i) use of all relevant sources of information for signal detection;
ii) appropriately applied methodology concerning analysis;
iii) appropriateness of investigations and follow-up actions, e.g. the implementation of recommendations following data review;
iv) implementation of the risk management plan (RMP), or other commitments, e.g., conditions of marketing authorisation;

6.2.2.4 Timely identification and provision of complete and accurate data to the Authority, in

particular in response to specific requests for data;

6.2.2.5 Implementation of approved changes to safety communications and product information, including internal distribution and external publication;

6.2.2.6 Interventional (where appropriate) and non-interventional clinical trials:

i) reporting suspected unexpected serious adverse reactions (SUSARs) and non-interventional study cases;
ii) receiving, recording and assessing cases from interventional and non-interventional trials (see ICSRs);
iii) submission of study results and relevant safety information and information included in PSURs, where applicable, particularly when associated with specific obligations or RMP commitments;
iv) appropriate selection of reference safety information, maintenance of investigator brochures and patient information with respect to safety;
v) the inclusion of study data in ongoing safety evaluation;

6.2.2.7 Pharmacovigilance system:

i) Roles and responsibilities of pharmacovigilance officer, e.g. access to the pharmacovigilance quality management system, the pharmacovigilance system master file, performance metrics, audit and inspection reports, and their ability to take action to improve compliance;
ii) the roles and responsibilities of the applicant/HCR in relation to the pharmacovigilance system;
iii) accuracy, completeness and maintenance of the pharmacovigilance system master file;
iv) quality and adequacy of training, qualifications and experience of staff;
v) coverage and adherence to the quality system in relation to pharmacovigilance, including quality control and quality assurance processes;
vi) fitness for purpose of computerised systems;
vii) contracts and agreements with all relevant parties appropriately reflect responsibilities and activities in the fulfilment of pharmacovigilance, and are adhered to.

6.2.3 The inspection may include pharmacovigilance quality management system for the fulfilment of conditions of registration and the implementation of risk– minimisation activities, as they relate to any of the above safety topics.

6.3 “For cause” Pharmacovigilance Inspections

6.3.1 "For cause" pharmacovigilance inspections are undertaken when a trigger is recognised, and an inspection is considered an appropriate way to examine the issues. “For cause” inspection require Pharmacovigilance officer involvement and awareness of product-specific issues; and in-depth examination of processes, decision-making, communications and actions relating to a specific trigger and/or product.

6.3.2 "For cause" inspections are more likely to focus on specific pharmacovigilance processes or to include an examination of identified compliance issues and their impact for a specific product. However, full system inspections may also be performed resulting from a trigger. "For cause" inspections may arise when, for example, one or more of the triggers listed below are identified:

6.3.2.1 Risk-benefit balance of the product:

i) Change in the risk-benefit balance where further examination through an inspection is

considered appropriate;

ii) Delays or failure to identify or communicate a risk or a change in the risk-benefit balance;

iii) Communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to SAHPRA.

6.3.2.2 Non-compliance or product safety issues identified during the monitoring of pharmacovigilance activities by SAHPRA;

i) Suspension or product withdrawal with no advance notice to SAHPRA;

6.3.2.3 Reporting obligations (expedited and periodic):

i) delays or omissions in reporting;

ii) poor quality or incomplete reports;

iii) inconsistencies between reports and other information sources;

6.3.2.4 Requests from the Authority:

iv) Failure to provide the requested information or data within the deadline specified by the Authority;

v) Poor quality or inadequate provision of data to fulfil requests for information from the Authority;

6.3.2.5 Fulfilment of commitments:

i) Concerns about the status or fulfilment of risk management plan (RMP) commitments;

ii) Delays or failure to carry out specific obligations relating to the monitoring of product safety, identified at the time of product registration;

iii) Poor quality of reports requested as specific obligations;

6.3.2.6 Inspections:

i) Delays in the implementation or inappropriate implementation of corrective and preventive actions;

ii) Information such as non-compliance or product safety issues from other types of inspections (GCP, GMP, GLP and GDP);

iii) Inspection information received from other authorities, which may highlight issues of non-compliance;

6.3.2.7 Others:

i) Concerns following review of the pharmacovigilance system master file;

ii) Non-inspection related information received from other authorities, which may highlight issues of non- compliance;

iii) Other sources of information or complaints.

6.4 Pre-authorisation Inspections

6.4.1 Pre-authorisation pharmacovigilance inspections are inspections performed before a registration certificate is issued. These inspections are conducted with the intent of examining the existing or proposed pharmacovigilance system as it has been described by the applicant/HCR in support of the registration application. Pre-authorisation inspections are not mandatory, however, the Authority may conduct it in specific circumstances where deemed necessary.

6.4.2 The following aspects shall be considered during the validation phase and/or early during the

assessment phase:

6.4.2.1 the applicant/HCR has not previously operated a pharmacovigilance system within the country or is in the process of establishing a new pharmacovigilance system;

6.4.2.2 previous information (e.g. inspection history and non-compliance notifications or information from other authorities) indicates that the applicant/HCR has a poor history or culture of compliance. If the applicant /HCR has a history of serious and/or persistent pharmacovigilance non-compliance, a pre-authorisation pharmacovigilance inspection may be conducted to confirm that improvements have been made to the system before a new authorisation is granted;

6.4.2.3 due to product-specific safety concerns, it may be considered appropriate to examine the applicant/HCR's ability:

i) to implement product specific risk-minimisation activities; or
ii) to meet specific safety conditions which may be imposed; or
iii) to manage routine pharmacovigilance for the product of concern (e.g., anticipated significant increase in adverse reaction reports when compared to other products).

6.4.3 In most cases, a risk assessment, based on a combination of product-specific and system-related issues, should be performed before a pre-authorisation pharmacovigilance inspection is requested.

6.4.4 If the outcome of the pre-authorisation inspection raises concerns about the applicant/HCR's ability to comply with the requirements laid down in the Regulations, the following recommendations may be considered:

i) non approval of registration application;
ii) a re-inspection prior to approval of registration certificate to confirm that critical findings and recommendations have been addressed;
iii) granting of the registration certificate with the recommendation to perform an early post-authorisation pharmacovigilance inspection. In this case, the findings would influence the timing of an inspection conducted as part of the Authority's routine programme of pharmacovigilance inspections;
iv) imposing of safety conditions on the registration certificate;

6.5 Re-inspections

6.5.1 A re-inspection may be conducted on a routine basis as part of a routine inspection programme. Risk factors should be assessed in order to prioritise re-inspections. Early re-inspection may take place where significant non-compliance has been identified and where it is necessary to verify actions taken to address findings and to evaluate ongoing compliance with the obligations, including evaluation of changes in the pharmacovigilance system. Early re-inspection may also be appropriate when it is known from a previous inspection that the inspected party had failed to implement appropriate corrective and preventive actions in response to an earlier inspection.

6.5.2 The scope of re-inspection will depend on inspection history. It may be appropriate to conduct a complete system review, for example, if a long time has elapsed since the previous inspection.

6.5.3 For the scope of a re-inspection, the following aspects should be considered:

i) review of the status of the system and/or corrective and preventive action plan(s) resulting from previous pharmacovigilance inspection(s);
ii) review of significant changes that have been made to the pharmacovigilance system since

the last pharmacovigilance inspection (e.g. change in the pharmacovigilance database, company mergers or acquisitions, significant changes in contracted activities, change in pharmacovigilance officer);

iii) review of process and/or product-specific issues identified from the assessment of information provided by the applicant/HCR, or not covered in a prior inspection.

iv) the results of an inspection should be provided to the inspected applicant/HCR, who should be given the opportunity to comment on any non-compliance identified.

6.6 Remote Inspections

6.6.1 These are pharmacovigilance inspections performed by inspectors remote from the premises of the applicant/HCR or manufacturers employed by the applicant/HCR.

6.6.2 Communication mechanisms such as the internet or telephone may be used in the conduct of the inspection. For example, in cases where key sites for pharmacovigilance activities are located outside the country or a third-party service provider is not available at the actual inspection site, but it is feasible to arrange interviews of relevant staff and review of documentation, including the safety database, source documents and PSMF, via remote access.

6.6.3 This approach may also be taken where there are logistical challenges to an on-site inspection during exceptional circumstances (e.g., a pandemic outbreak or travel restrictions). Such approaches are taken at the discretion of the inspectors. The logistical aspects of the remote inspection should be considered following liaison with the applicant/HCR. Where feasible, a remote inspection may lead to a visit to the inspection site if it is considered that the remote inspection has revealed issues, which require on-site inspection, or if the objectives of the inspection could not be met by remote inspection.

6.7 Post-authorisation Inspections

6.7.1 Post-authorisation pharmacovigilance inspections are inspections performed after a registration certificate is issued and are intended to examine whether the applicant/HCR complies with its pharmacovigilance obligations. They can be any of the above mentioned types.

7. INSPECTION PROCESS

7.1 Inspection planning

7.1.1 Pharmacovigilance inspection planning should be based on a systematic and risk-based approach to make the best use of surveillance and enforcement resources whilst maintaining a high level of public health protection. A risk-based approach to inspection planning will enable the frequency, scope and extensiveness of inspections to be determined accordingly.

7.1.2 In order to ensure that inspection resources are used in an efficient way, the scheduling and conduct of inspections should be driven by the preparation of inspection programmes. Sharing of information and communication between inspectors and assessors at the pharmacovigilance unit is important to ensure successful prioritisation and targeting of these inspections.

7.2 Factors to consider

7.2.1 Factors which may be taken into consideration, as appropriate, by SAHPRA when establishing pharmacovigilance inspection programmes include, but are not limited to:

7.2.1.1 Inspection related:

i) compliance history identified during previous pharmacovigilance inspections or other types of inspections (GCP, GMP, GLP and GDP);
ii) re-inspection date recommended by the inspectors or assessors/reviewers as a result of a previous inspection;

7.2.1.2 Product related:

i) product with additional pharmacovigilance activities or risk-minimization activities;
ii) authorisation with conditions associated with safety, e.g. requirement for local post-authorisation safety studies (PASS) or designation for additional monitoring as part of the pharmacovigilance plan;
iii) product(s) with large sales volume, i.e. products associated with large patient exposure in South Africa;
iv) product(s) with limited alternative in the market place;

7.2.1.3 Applicant/HCR related:

i) applicant/HCR that has never been subjected to a pharmacovigilance inspection;
ii) applicant/HCR with many products on the market in South Africa;
iii) resources available to the applicant/HCR for the pharmacovigilance activities they undertake;
iv) applicant/HCR with no previous health products registered in South Africa;
v) negative information and/or safety concerns raised by SAHPRA, other bodies outside South Africa or other areas (i.e. GCP, GMP, GLP and GDP);
vi) changes in the applicant/HCR organisation, such as mergers and acquisitions;

7.2.1.4 Pharmacovigilance system related:

i) applicant/HCR with sub-contracted pharmacovigilance activities (function of the pharmacovigilance officer in South Africa, reporting of safety data etc.) and/or multiple manufacturers employed to perform pharmacovigilance activities;
ii) change of pharmacovigilance officer since the last inspection;
iii) changes to the pharmacovigilance safety database(s), which could include a change in the database itself or associated databases, the validation status of the database as well as information about transferred or migrated data;
iv) changes in contractual arrangements with pharmacovigilance service providers or the sites at which pharmacovigilance is conducted;
v) delegation or transfer of pharmacovigilance system master file management.

7.3 Sites to be inspected

7.3.1 Any party carrying out pharmacovigilance activities in whole or in part, on behalf of, or in conjunction with the applicant/HCR may be inspected, in order to confirm their capability to support the applicant/HCR's compliance with pharmacovigilance obligations.

7.3.2 Inspections of sites outside South Africa might be appropriate where the main pharmacovigilance centre, databases and/or activities are located outside South Africa and it would be otherwise inefficient or impossible to confirm compliance from a site within South Africa.

7.3.3 The type and number of sites to be inspected should be selected appropriately to ensure that the key

objectives within the scope of the inspection are met.

7.4 Inspection Scope

7.4.1 The inspection scope will depend on the objectives of the inspection as well as the coverage of any previous inspections by the Authority and whether it is a system or product-related inspection

7.4.2 The following elements should be considered when preparing the scope of the inspection, as applicable:

i) information supplied in the pharmacovigilance system master file;
ii) information concerning the functioning of the pharmacovigilance system, e.g. compliance data available from the applicant/HCR such as reporting and data quality audits;
iii) specific trigger;
iv) Additional data to be requested in advance of an inspection in order to select appropriate sites or clarify aspects of the pharmacovigilance system.

7.5 Grading of inspection findings

7.5.1 Deficiencies found during the Authority's pharmacovigilance inspections are graded as follows:

7.5.1.1 **Critical**: A deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of Medicines and Related Substance Act (Act 101 of 1965) as amended and applicable SAHPRA guidelines. Deficiencies classified as critical may include a pattern of deviations classified as major. A critical deficiency also occurs when applicant/HCR is observed to have engaged in fraud, misrepresentation or falsification of data.

7.5.1.2 **Major**: A deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of Medicines and Related Substance Act (Act 101 of 1965) as amended and applicable SAHPRA guidelines. Deficiencies classified as major may include a pattern of deviations classified as minor.

7.5.1.3 **Minor**: A deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

7.5.2 An inspection report is then prepared and reviewed internally to ensure consistency of classification of deficiencies prior to issue of the final report. The report will be shared with the applicant/HCR usually within calendar 30 calendar days of the site visit or the date of the provision of the last document requested. It should be noted that the factual matter contained in the inspection report relates only to those things that the inspection team sees and hears during the inspection process.

7.6 Responding to Findings

7.6.1 Following the issue of the inspection report, the applicant/HCR is requested to respond to any deficiencies identified and to provide the Authority with an appropriate corrective action and preventative action plan (CAPA) within 30 calendar days or a deadline to be determined by the Authority based on the magnitude of non-compliance identified. The applicant/HCR may be required to provide reports and where necessary evidence of the progress and completion of the action plan. There may be re-inspection at an appropriate time to verify the progress and success of these remedial

actions.

7.6.2 In certain circumstances, the applicant/HCR may be required to take immediate action to address critical or major findings, for the protection of public health and safety. Where required, evidence of completion of all CAPAs should be submitted to the Authority not later than 30 calendar days following their completion.

7.7 Inspection follow-up

7.7.1 When non-compliance with pharmacovigilance obligations is identified during an inspection, follow-up should be done until a corrective and preventive action plan is completed.

7.7.2 The following follow-up actions should be considered, as appropriate:

i) review of the applicant/HCR's corrective and preventive action plan;
ii) review of the periodic progress reports, when deemed necessary;
iii) re-inspections, to assess appropriate implementation of the corrective and preventive action plan;
iv) requests for submission of previously un-submitted data; submission of variations, e.g. to amend product information; submission of impact analyses, e.g., following review of data that were not previously considered during routine signal detection activities;
v) requests for issuing safety communications, including amendments of marketing and/or advertising information;
vi) requests for a meeting with the applicant/HCR to discuss the deficiencies, the impact of the deficiencies and action plans;
vii) communication of the inspection findings to other regulatory authorities outside South Africa;
viii) other product-related actions depending on the impact of the deficiencies and the outcome of follow-up actions (this may include recalls or actions relating to the registration certificate).
ix) where required, evidence of completion of all CAPAs should be submitted to the Authority not later than 30 calendar days following their completion.

8. ROLES AND RESPONSIBILITIES OF THE APPLICANT/HCR

8.1 The applicant/HCR must have permanently and continuously at its disposal a Qualified Person Responsible for Pharmacovigilance (QPPV) for all products, old or registered and marketed in South Africa. The QPPV should reside and operates in South Africa and is responsible for the establishment and maintenance of the local pharmacovigilance system. (Please refer to the *Pharmacovigilance Systems* guideline for more details on the QPPV requirements).

8.2 The HCR shall ensure that the QPPV/local Pharmacovigilance Officer has adequate theoretical and practical knowledge for the performance of pharmacovigilance activities. The QPPV/local Pharmacovigilance Officer should have skills for 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.

8.3 All applicants/HCRs with registered products and those who have submitted new applications are subject to pharmacovigilance inspections. Therefore, both have responsibilities in relation to inspections, including but not limited to the following:

i) to be always inspection-ready as inspections may be unannounced;
ii) to maintain and make available to the inspectors on request, no later than 14 calendar days after the receipt of a request, the pharmacovigilance system master file as required.
iii) to ensure that the sites selected for inspection, which may include firms contracted by the applicant/HCR to perform pharmacovigilance activities, agree to be pre-inspected before the inspection is performed;
iv) to make available to the inspectors any information and/or documentation required for the preparation of the inspection within the deadline given or during the conduct of the inspection;
v) to ensure that relevant staff involved in pharmacovigilance activities or related activities are present and available during the inspection for interviews or clarification of issues identified;
vi) to ensure that relevant pharmacovigilance data is accessible from at least one point;
vii) to ensure that appropriate and timely corrective and preventive action plans are implemented to address findings observed during an inspection, with appropriate prioritization of critical and/or major findings.

9. REGULATORY ACTIONS AND SANCTIONS

9.1 SAHPRA is obliged to ensure compliance with pharmacovigilance obligations in order to protect South African public health. When non-compliance with pharmacovigilance obligations is detected, the necessary action should be taken on a case-by-case basis.

9.2 The action to be taken should depend on the potential negative public health impact of the non-compliance(s), but any instance of non-compliance may be considered for enforcement action.

9.3 The necessary measures to ensure that the applicant/HCR is subject to effective, proportionate and dissuasive penalties should be in place.

9.4 In the event of non-compliance, possible regulatory options include the following, in accordance with guidance and, as applicable, rules set in legislation:

i) Education and facilitation: the Authority may communicate with the applicant/HCR representatives (e.g., in a meeting) to summarise the identified non-compliances, to clarify the legal requirements and the expectations of the regulator, and to review the applicant/HCR's proposals for corrective and preventive actions;
ii) Re-inspection: non-compliant applicant/HCR may be re-inspected to ensure compliance is achieved;
iii) Warning letter, non-compliance statement, etc.: these are non-statutory or statutory instruments in accordance with national legislation which SAHPRA may issue stating the legislation and guideline that has been breached, reminding the applicant/HCR of their pharmacovigilance obligations or specifying the steps that the applicant/HCR must take and in what timeframe in order to rectify the non-compliance and to prevent a further case of non-compliance;
iv) Actions against applicant/HCR or registration application(s) e.g.;
- variation of the registration certificate;
- suspension or revocation of the registration certificate;
- delays in approvals of new registration applications until corrective and preventive actions have been implemented or the addition of safety conditions to new registration;
- requests for pre-authorisation inspections;

v) Product recalls e.g. where important safety warnings have been omitted from product information;
vi) Action relating to marketing or advertising information;
vii) Administrative penalties, usually fixed fines or based on company profits or levied on a daily basis;

viii) Referral for criminal prosecution with the possibility of imprisonment (in accordance with national legislation).

10. INSPECTION FEES

10.1 Pharmacovigilance inspection fee(s) (and inspectors' expenses where applicable) will be charged in accordance with the fees published by the Authority.

11. TRANSPARENCY

11.1 Information on the conduct and outcome of pharmacovigilance inspections and their follow-up may be made publicly available.

12. REFERENCES

12.1 Adapted from: Guideline on good pharmacovigilance practices (GVP): Pharmacovigilance inspections – Module III (Rev 1) EMA/119871/2012 Rev 1

12.2 Food and Drug Authority Ghana. Guideline for conducting pharmacovigilance inspections. FDA/SMC/SMD/GL- PVI/