Botswana Medicines Regulatory Authority

Approved By: _____ _____

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Revision status sheet

Page	Changes made	Issue No.	Process owner	Reviwer's name	Date
16	4.6 Amended section 4.6 to add the manufacturers and/or MAHs should inform the NRA of any safety signal, significant safety information of a medicinal product registered in Botswana as well as any marketing or regulatory decisions taken in the country of origin or other countries where the product is marketed.	2.0	Director-Pharmacovigilance and clinical trials	Pono Pono	21/09/2023
18	Existing section 4.9 was deleted because the information was incomplete. The section was replaced with new and appropriate information; 4.9 **Dear Healthcare Professional Letters 4.9.1 Contents of a DHCP letter, 4.9.2 Submission of DHCP letter**	2.0	Director-Pharmacovigilance and clinical trials	Pono Pono	29/12/2023
All pages	Change in document number from BOMRA/PMS/PMS/P02/G02 to BOMRA/PCT/PV/P01/G02	1.0	Director-Pharmacovigilance and clinical trials	Pono Pono	06/12/2022
8	Pharmacovigilance system for MAHs- section 4.3.1 and 4.3.2 added.	1.0	Director-Pharmacovigilance and clinical trials	Pono Pono	12/05/2022
9	section 4.3.4, 4.3.5 and 4.3.6 were added.	1.0	Director-Pharmacovigilance and clinical trials	Pono Pono	12/05/2022
10	section 4.3.7 and 4.3.8 were added.	1.0	Director-Pharmacovigilance and clinical trials	Pono Pono	12/05/2022
11	section 4.3.9, and 4.3.10 were added.	1.0	Director-Pharmacovigilance and clinical trials	Pono Pono	12/05/2022
13	Elements of routine inspections added	1.0	Director-Pharmacovigilance and clinical trials	Pono Pono	12/05/2022

17	Section 4.8 Submission of Development Safety Update Reports (DSURs) was added	1.0	Director-Pharmacovigilance and clinical trials	Pono Pono	12/05/2022
21	5.0 Reliance in Pharmacovigilance added	1.0	Director-Pharmacovigilance and clinical trials	Pono Pono	12/05/2022

1 Purpose

The purpose of this document is to provide guidance to Market Authorisation Holders (MAHs) on pharmacovigilance activities of their medical products approved for sale and use in Botswana.

2 Scope

The scope of this guideline includes pharmacovigilance activities for approved medical products in post-authorisation phase in Botswana. Matters under scope include:

a) The reporting of safety information (ICSRs, PBRER, emerging safety issues, safety decisions from foreign NRAs
b) Pharmacovigilance inspections.

3 Definitions and abbreviations

3.1 Definition

The following definitions shall apply:

3.1.1 Adverse Drug Reactions (ADR) -a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function.

3.1.2 Adverse Event (AE) or Experience - any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

3.1.3 Applicant - means a company or individual who applies for the registration of a product or a medicine or who has applied for the use of a medicine or product in a clinical trial in Botswana.

3.1.4 Clinical Trial - any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

3.1.5 Emerging Safety Issue -a safety issue considered by a marketing authorisation holder to require urgent attention by the competent authority because of the potential major impact on the risk-benefit balance of the medicinal product and/or on patients' or public health, and the potential need for prompt regulatory action and communication to patients and healthcare professionals.

3.1.6 Individual Case Study Report (ICSR) - an adverse event report for an individual patient.

3.1.7 Lack of Efficacy – failure of the medicine to produce the expected pharmacological action.

3.1.8 Market Authorization Holder (MAH)- a Marketing Authorization Holder (MAH) is a company, firm or non-profit organization that has been granted a marketing authorization.

3.1.9 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, alleviation, modification or prevention of disease, illness, abnormal physical or organic condition or the symptoms thereof restoring, correcting, or modifying any somatic or psychic or organic condition.

3.1.10 National Medicines Regulatory Authority (NRA) - Botswana Medicines Regulatory Authority (BoMRA) in an NRA and NPVC is located within BoMRA.

3.1.11 National Pharmacovigilance Centre (NPVC) - WHO-approved pharmacovigilance center in countries participating in the WHO Program for International Drug Monitoring and is usually a part of or closely linked to the national drug regulatory agency i.e., BoMRA for Botswana.

3.1.12 Pharmacovigilance (PV) - the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

3.1.13 Serious Adverse Events (SAE) - any untoward medical occurrence that at any dose results in death, life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

3.1.14 Side Effects - any unintended effect of a pharmaceutical product occurring at doses normally used in humans which is related to the pharmacological properties of the drug.

3.1.15 Signal - Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than one report is required to generate a signal depending on the seriousness of the event and the quality of the information.

3.1.16 Unexpected Adverse Reaction - an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product.

3.1.17 WHO-UMC – WHO Collaborating center for International Drug Monitoring – Uppsala Monitoring Centre

3.1.18 Post-Authorization Safety Study (PASS) - any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

3.1.19 Legal Technical Representative - an individual appointed by MAH to oversee all safety issues pertaining to their products. A single Legal Technical Representative can be responsible for more than one company.

3.1.20 PV Focal Point - n individual appointed by the Legal Technical Representative for all safety issues pertaining to their products.

3.1.21 Minor variations - are changes that may have minor effects on the overall safety, efficacy and quality of the FPP.

3.1.22 Major variations – are changes that could have major effects on the overall safety, efficacy and quality of the FPP.

3.2 Abbreviations

The following abbreviations shall apply;

3.2.1 ADR – Adverse Drug Reaction
3.2.3 HCP – Health Care Professionals
3.2.3 ICSR – Individual Case Safety Report
3.2.4 MAH – Market Authorization Holder
3.2.5 PSUR – Periodic Safety Update Report
3.2.6 PV – Pharmacovigilance
3.2.7 QPPV– Qualified Person responsible for Pharmacovigilance
3.2.8 SADC–Southern Africa Development Community
3.2.9 SAE – Serious Adverse Events
3.2.10 WHO-UMC –World Health Organization – Uppsala Monitoring Centre
3.1.11 PASS – Post authorization safety study
3.1.12 RMP – Risk Management Plan document
3.1.13 PBRER – Periodic Benefit Risk Evaluation Report according to the most recent version of the E2C guideline
3.1.14 LTR- Legal Technical Representative
3.1.15 SmPC- Summary of Product Characteristics

4. Introduction

Adverse Drug Reaction (ADR) reporting, and monitoring system is essential to collect, collate and analyze ADR data as a means of establishing new knowledge and generate early signals of possible medicine related complications not reported through clinical trials. Output from such ADR reporting systems complement the information appearing in the published literature and from other studies. Collection, collation, and analysis of suspected ADRs at the national level is of paramount importance for the continuous improvement of clinical practice, therefore market authorization holders have the responsibility to monitor the safety of their products in the market.

4.1 Legal Provision

Section 32 of MRSA, 2013 requires that MAHs report ADRs to the Authority.

4.2 ADR Reporting Timelines by MAHs to BoMRA

ADR reports made to an MAH either during a study or through spontaneous report must be sent to BoMRA via email (reportadr@bomra.co.bw). Each report must bear a unique reference number for easy linking with the follow-up report.

ICSR submission format

MAHs are expected to submit ICSRs in the format of XML files containing ICSR data according to the ICH-E2B(R3) standard.XML files in E2B(R2) format may be acceptable upon BoMRA agreement. MAHs lacking any E2B system can submit CIOMS-I forms.

ICSR reported from Botswana must be reported to BoMRA according to the following timelines according to ICH E2A and E2D Guidelines:

Table 1. ICSR and submission deadlines

Post Authorization ICSRs	**Domestic**
Death or Life threatening	As soon as possible, no later than 15 days
Other serious	As soon as possible, no later than 15 days (a)
Nonserious	Within 90 days (b)
(a): according to ICH-E2D Guideline (b): according to EU-GVP Guideline Module VI	

4.2.1 After Initial receipt of an adverse reaction report, a notice of acknowledgement will be sent to the LTR/QPPV by the pharmacovigilance officer. Any follow-up correspondence from the reporter, relating to the same case report should be cross-referenced to the appropriate reference number assigned by the applicant (relating specifically to the initial notification). This is to minimize the duplication of reports submitted by applicants.

4.2.2 Foreign ICSRs (ADRs/AE occurring outside Botswana) should NOT be forwarded to BoMRA on a routine basis but should be reported in the context of a specific safety issue or on request by BoMRA. BoMRA should be advised of any emerging safety issue or action, which has been taken by any foreign agency, including the basis for such an action, within 5 calendar days of first knowledge by MAH. Safety related withdrawal/suspension of the registration status in any country should also be notified within 48-72 HOURS of first knowledge by the MAH.

4.2.3 If the MAH receives a report of a suspected adverse reaction to a medicine marketed by another applicant, such a report should promptly be forwarded to the respective applicant. Such reports should not be reported to the Authority by the MAH to whom the event was originally reported to. When serious, unexpected reactions are observed for another applicant's medicine, used during the conduct of clinical trial, reports should be submitted directly to the authority by the applicant conducting the study.

An E-mail id of MAH or their authorized representative shall be provided in the promotional material to report ADRs.

4.3 Pharmacovigilance system for MAHs

In accordance with Good Pharmacovigilance Practices, all MAHs must establish an appropriate system of pharmacovigilance (PV) in the company. This is a way the company demonstrates that it accepts responsibility and liability for its products on the market and their safe use.

4.3.1 A pharmacovigilance system is defined as a system used by MAH to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of medicinal products approved by BoMRA and to detect any changes to their benefit-risk balance. The system should cover MAH's organizational structure i.e. organogram describing PV personnel's roles and responsibilities, procedures, processes and resources of the PV system as well as appropriate resource management, compliance management and record management.

The quality system shall 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.
d) Quality improvements: correcting and improving the structures and processes wherever necessary.

4.3.2 The objectives for PV system shall be to comply with legal requirements for PV tasks and responsibilities, prevention from adverse events, promotion of safe and effective use of medical products and protection of patients and public health.

4.3.3 The PV system at MAH should at least consist of the following:

a) Product safety data and Individual ADR/AE reports collection and data management.
b) Signal detection mechanism for new or changing safety issues.
c) Data evaluation system (benefit-risk monitoring i.e. including signal detection, aggregate data review, etc.) and decision making with regards to safety issues.
d) Pro-active risk management and risk minimization plans and actions (including regulatory action) to protect public health
e) Communication with stakeholders (any communication related to safety concerns of the products should always be in consultation and consensus with BoMRA)
f) Quality assurance audits of the key processes, outcomes and actions taken.

4.3.4 Responsibilities for the quality system within an organization

MAH shall have a sufficient number of competent and appropriately qualified and trained personnel shall be available for the performance of pharmacovigilance activities.

For the purpose of a systematic approach towards quality in accordance with the quality cycle, managerial in any organization should be responsible for:

a) Ensuring that the organization 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 PV system, including its quality system at regular intervals in risk-based manner to verify its effectiveness and introducing corrective and preventative measures wherever necessary
h) Ensuring that mechanism exist for timely and effective communication, including escalation processes of safety concerns relating to medical products within an organization
i) Identifying and investigating concerns arising within an organization regarding suspected non-adherence to the requirements of the quality and PV system and taking corrective, preventative, and escalation action as necessary
j) Ensuring that audits are performed
k) Assigning roles, responsibilities, and authorities to staff members according to their competencies and communicating and implementing these throughout the organization.

4.3.5 Training of MAH personnel for PV

a) All personnel involved in the performance of PV activities shall receive initial and continued training. This training shall relate to the roles and responsibilities of the personnel and start within one month of joining.
b) The organization shall keep training plans and records for documenting, maintaining, and developing the competences of personnel. Training plans should be based on training needs assessment and should be subject to monitoring.

4.3.6 Facilities and equipment for pharmacovigilance

a) The MAH shall maintain facilities and equipment used to support PV processes. These include office space, Information technology systems and storage space (electronic).
b) They should be located, designed, constructed, adapted, and maintained to suit their intended purpose in line with the quality objectives for PV.
c) Facilities and equipment which are critical for the conduct of PV should be subject to appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose.
d) In case of outsourcing PV activities to a third-party person or external organization, a detailed pharmacovigilance contract or agreement shall be in place.

4.3.7 Quality Procedures and Processes

For compliance management, MAHs shall have a system to ensure:

a) continuous monitoring of pharmacovigilance data, the examination of options for risk minimisation and prevention and those appropriate measures are taken by the marketing authorisation holder
b) the scientific evaluation of all information on the risks of medicinal 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 marketing authorisation or associated with occupational exposure
c) the submission of accurate and verifiable data on serious and non-serious adverse reactions to the competent authorities within the legally required time-limits
d) the quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signals
e) effective communication by the marketing authorisation holder with BoMRA, including communication on new or changed risks, the pharmacovigilance system master file, risk management systems, risk minimisations measures, periodic safety update reports, corrective and preventive actions, and post-authorisation safety studies
f) the update of product information by the marketing authorisation holder in the light of scientific knowledge
g) appropriate communication of relevant safety information to healthcare professionals and patients

4.3.8 Record management and documentation

The MAH shall record all PV information and ensure that it is handled and stored so as to allow acute, reporting, interpretation and verification of the information.
A record management system shall 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.

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 medicinal products, in accordance with the applicable retention periods.

As part of a record management system, specific measures should be taken at each stage in the storage and processing of PV data to ensure data security and confidentiality. This should involve strict limitation of access to documents and to databases to authorized personnel respecting the medical and administrative confidentiality of the data. The hard copies should for a minimum of 10 years and soft copies to be stored indefinitely.

4.3.9 Critical pharmacovigilance processes

The following pharmacovigilance processes should be considered as critical include:

a) continuous safety profile monitoring and benefit-risk evaluation of authorised medicinal products;
b) establishing, assessing, and implementing risk management systems and evaluating the effectiveness of risk minimisation
c) 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;
d) signal management;
e) scheduling, preparation (including data evaluation and quality control), submission and assessment of periodic safety update reports;
f) meeting commitments and responding to requests from competent authorities, including provision of correct and complete information;
g) interaction between the pharmacovigilance and product quality defect systems;
h) communication about safety concerns between marketing authorisation holders and competent authorities, in particular notifying changes to the risk-benefit balance of medicinal products;
i) communicating information to patients and healthcare professionals about changes to the risk-benefit balance of products for the aim of safe and effective use of medicinal products;
j) keeping product information up-to-date with the current scientific knowledge, including the conclusions of the assessment and recommendations from the applicable competent authority;
k) implementation of variations to marketing authorisations for safety reasons according to the urgency required.

4.3.10 Pharmacovigilance System Master File

Every MAH shall have pharmacovigilance master plan that includes safety specifications and PV plan. The plan shall be developed by the MAH and can be discussed with the authority during product development where practicable, prior to approval of a new product, or when a safety concern arises post marketing.

The MAH holder should be capable of providing the pharmacovigilance system master file within 7 business days, after the receipt of a request from BoMRA.

4.4 Qualified Person for Pharmacovigilance

MAH shall have QPPV for PV activities. This person should have experience in all aspects of PV. MAH must provide the BoMRA with the details of the QPPV (including full name, postal address, email address, telephone, and fax numbers). Any changes of these details should be promptly advised. QPPV shall be based in the SADC region and act as the contact point for the Authority for PV issues, should be easily contactable.

Note: QPPV should have acquired adequate theoretical and practical knowledge for the performance of pharmacovigilance activities. He/she 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.

4.5 Inspections of Pharmacovigilance system at Market Authorization Holders

This provides insight into planning, conducting, reporting and follow up of PV inspections by regulatory authorities/ officials responsible for inspection to improve /assure PV process.
All MAHs shall identify a Legal Technical Representative who should have a registered premises within Botswana, who is responsible for Safety monitoring and communications for the product. A single Legal Technical Representative can be responsible for more than one company.

Feedback to Market Authorization Holders

The Authority will provide inspection report within 60 working days after completion of the inspection.

4.5.1 Objectives

The objectives of PV inspections are:

a) To verify by examination and evidence, the appropriateness and effectiveness of the implementation and operation of the PV system
b) To find evidence and help evaluating the evidence objectively to determine the extent to which the audit criteria are fulfilled and contributing to the improvement, control, and governance of the PV process
c) To assess and establish that the MAH has qualified personnel, robust system, and facilities to conduct PV activities
d) To identify, record and address non-compliance which may pose a risk to public health
e) To take regulatory action wherever considered necessary, based on the result of the inspection.

4.5.2 Inspection Types

The inspections shall include system and product-related inspections, routine inspections and "for cause" inspections, Pre-and Post authorisation inspections, announced and unannounced inspections, re-inspections, and remote inspections.

4.5.2.1 Routine inspection

These are scheduled in advance as part of inspection programmes. They 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. The focus of these inspections is to determine that the MAH personnel, systems, and facilities are in place to meet their regulatory PV obligations for the marketed medical products in Botswana. These inspections will be prioritized based on the potential risk to public health, the nature of the products, the extent of use, number of products that the MAH has in the market.

Routine inspections could include the following elements, as appropriate:

i. Individual Case Safety Reports (ICSRs)
    a) collecting, receiving, and exchanging reports
    b) assessment, including mechanisms for obtaining and recording reporter assessments, company application of event terms, seriousness, expectedness, and causality.
    c) follow-up and outcome recording, for example final outcome of cases of exposure in pregnancy and medical confirmation of consumer reported events

d) reporting according to the requirements for various types of reported ICSRs, including onward reporting to the relevant bodies and timeliness of such reporting;
e) record keeping and archiving for ICSRs;

ii. Periodic Safety Update Reports (PSURs)
a) completeness and accuracy of the data included, appropriateness of decisions concerning data that are not included;
b) addressing safety topics, providing relevant analyses and actions;
c) formatting according to requirements
d) timelines of submissions

iii. Ongoing safety evaluation
a) use of all relevant sources of information for signal detection;
b) appropriately applied methodology concerning analysis;
c) appropriateness of investigations and follow-up actions, e.g. the implementation of recommendations following data review;
d) implementation of the RMP, or other commitments, e.g. conditions of marketing authorisation;
e) timely identification and provision of complete and accurate data to the competent authority(ies), in particular in response to specific requests for data;
f) implementation of approved changes to safety communications and product information, including internal distribution and external publication;

iv. Interventional and non-interventional clinical trails
a) reporting suspected unexpected serious adverse reactions (SUSARs) according to Directive 2001/20/EC and non-interventional study cases according to Directive 2001/83/EC;
b) receiving, recording and assessing cases from interventional and non-interventional trials (see ICSRs);
c) submission of study results and relevant safety information (e.g. development safety update reports (DSURs) and information included in PSURs), where applicable, PASS or post-authorisation efficacy studies (PAES) submissions, particularly when associated with specific obligations or RMP commitments;
d) appropriate selection of reference safety information, maintenance of investigator brochures and patient information with respect to safety;
e) the inclusion of study data in ongoing safety evaluation

v. Pharmacovigilance system
a) QPPV roles and responsibilities, e.g., access to the quality system, the pharmacovigilance system master file, performance metrics, audit and inspection reports, and their ability to take action to improve compliance;
b) the roles and responsibilities of the marketing authorisation holder in relation to the pharmacovigilance system;
c) accuracy, completeness and maintenance of the pharmacovigilance system master file which shall be permanently and immediately available for inspection at the site where it is kept;
d) quality and adequacy of training, qualifications and experience of staff;
e) coverage and adherence to the quality system in relation to pharmacovigilance, including quality control and quality assurance processes;

f) fitness for purpose of computerised systems;
g) contracts and agreements with all relevant parties appropriately reflect responsibilities and activities in the fulfillment of pharmacovigilance and are adhered to.

vi. May include the system for the fulfillment of conditions of a marketing authorization and the implementation of risk-minimization activities, as they relate to any of the above safety topics.

4.5.2.2 For Cause inspections

These types of inspections may be considered as and when there is a trigger and BoMRA determines that inspection is the appropriate way to examine the issues. Triggering factors that may lead to such inspections are listed below (but not limited to):

a) Continuous delays or omission or poor-quality reporting of ICSRs/PSURs/RMPs.
b) Failure to provide the requested information or data within the deadline specified by the regulatory authority
c) Delays or failure to carry out specific obligations relating to the monitoring of pharmaceutical product safety, identified at the time of marketing authorization
d) Delays in the implementation or inappropriate implementation of CAPAs
e) Inspections information received from other authorities, which may highlight issues of non-compliance
f) Sudden product withdrawal.

4.5.2.3 Pre-authorization inspections

Pre-authorisation pharmacovigilance inspections are inspections performed before a marketing authorisation is granted. These inspections are conducted with the intent of examining the existing or proposed pharmacovigilance system as it has been described by the applicant in support of the marketing authorisation application. Pre-authorisation inspections are not mandatory but may be requested in specific circumstances determined by BoMRA. (From The EMA GVP).

4.5.3 Inspection Procedure

4.5.3.1 Inspection planning

PV inspections will be based on a systematic and risk-based approach to make the best 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 and scope of inspections to be determined accordingly. PV inspections will be done by the BoMRA officials responsible for PV inspections.

4.5.3.2 Organizations to be inspected

Any party carrying out PV activities in whole or in part, on behalf of, or in conjunction with the MAH may be inspected, in order to confirm their capabilities to support the MAH 's compliance with PV obligations.

4.5.3.3 Inspection procedures

The inspection procedures depend on the nature of the inspection and the conditions of inspection. All the necessary PV documents (Annexure 2) should be submitted to the inspectors during inspection, including the PSMF which will be used to inform inspection

conduct. When necessary, the inspectors may also request other documents containing related information. The MAH shall ensure that relevant staff, other than QPPVs, involved in pharmacovigilance activities or related activities are present and available during the inspection for interviews or clarification of issues identified.

4.5.3.4 Inspection findings

Each inspection will result in an inspection report and the findings shall be classified into critical, major, and minor. The results of an inspection shall be made available to the PV department of the inspected entity. The MAH who will be given the opportunity to comment on any non-compliance identified within timelines prescribed by BoMRA. Any non-compliance shall be rectified in a timely manner through the implementation of a corrective and preventive action plan.

a) **Critical**- Fundamental weakness in the PV System or practices that adversely deviate from the PV regulations of BoMRA and or affect the rights and safety of patients or poses a potential risk to the public.

b) **Major** -It is an insignificant weakness in one or more PV processes or practice or a fundamental weakness in part of one or more PV process or practices that is detrimental to the whole process and could potentially adversely affect the rights, safety, or wellbeing of patients.

c) **Minor** - It's a weakness in the part of one or more PV processes or practices that is not expected to adversely affect the whole PV system or process and or rights, safety, or wellbeing of patients.

4.5.3.5 Inspection follow up

The following follow up actions should be considered as appropriate:

a) Review of the MAH's CAPA plan
b) Review of the periodic progress when deemed necessary
c) Re-inspection to assess appropriate implementation of the corrective and preventative plan
d) Request for submission of previously un-submitted data, submission of variations
e) Request for issuing safety communications including amendments of marketing and or advertising information
f) Communication of the inspection findings to other regulatory authorities
g) Regulatory actions

4.5.3.6 In the event of non-compliance

When non-compliance with PV obligations is identified during an inspection, follow-up will be required until a CAPA is completed. Any non-compliance should be rectified by the MAH within three (3) months through the implementation of the CAPA plan.

In the event of non-compliance, possible regulatory options include the following:

a) Updating of package inserts /SmPC

b) Product recalls
c) Suspension/cancellation /withdrawal of marketing authorization
d) Amendments or suspension of clinical trials due to product-specific safety issues
e) Restriction on approvals of new marketing authorization applications

4.6 Requirements for reporting adverse events reporting by MAH

All MAH shall report to BoMRA any adverse reaction/events suspected to be associated with the use of their products notified to them by healthcare professionals, patients, and consumers.
The adverse events reports shall include reports that arise from post-marketing experience, unsolicited and solicited sources, clinical trials, non-interventional post-registration studies and other post marketing and programs (see annex 1 for reporting timelines).

4.6.1 Submission of Periodic Benefit Risk Evaluation Reports / Periodic Safety Update Reports

This is a periodic report produced by a MAH intended to provide an update of a worldwide safety experience of a licensed medicinal product to BoMRA at defined times post marketing authorization. This should be submitted in ICH E2C most recent revision format including appendices. The PSURs or PBRERs should be submitted in a CD. It should be labelled; Name of MAH and Term "PSURs or PBRERs". Online submissions must be emailed to records@bomra.co.bw .

PSURs/PBRERs are reports that reflect the changes in safety, quality and effectiveness profile of the product are to be submitted to BoMRA as part of the new application for registration. Any changes should be highlighted by the MAH to BoMRA in writing including the appropriate regulatory action taken already by the country of origin or other countries, or to be taken. Pharmacovigilance plan for the product in line with its risk management plan where applicable also to be submitted. After registration of the product in Botswana, PSURs/PBRERs should be submitted to BoMRA at defined time intervals with specific national regional annexure (African region).

The periodic safety update report shall contain a minimum of the following:
a) Summaries of data relevant to benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorization
b) A scientific evaluation of the risk-benefit balance of the medicinal product
c) All data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorization holder relating to the volume of prescriptions, including an estimate of population exposed to the medicinal product
d) Collection of ADR/AE information (i.e., local, and foreign serious and or nonserious ADRs/AE, case reports published on international or local literatures including academic conferences).
e) Updated Summary of product characteristics or product information, patient information leaflet and company core data sheet.

4.7 Timelines for PSUR AND PBRERs Submission

Submission of PSUR/PBRERs for newly registered medicinal products in Botswana should be submitted every 6 months for the first 2 years after approval and later annually for the next two years and thereafter at the time of product marketing authorization renewal.

For generics and medicinal products registered for 5 years or more in Botswana, their PSURs/PBRER must be submitted at the time of product marketing authorization renewal. However, the MAH may be notified by BoMRA to submit PSURs/PBRERs in the intervals between the marketing authorization renewals, if required. Submission of PBRERs/PSUR may be aligned with global submission in consultation and consensus with BoMRA.

The PSUR/PBRER should have an executive summary briefing/describing the implications of the safety issues observed for Botswana population and highlighting the reactions, safety signals and risks observed in the national populations. The authority shall provide feedback within 90 working days after the submission of PSUR/PBRER.

4.8 Dear Healthcare Professional Letters

4.8.1 Contents of a DHCP letter, 4.9.2 Submission of DHCP letter

New or updated information about medicinal products emerges throughout its product's life cycle. As a result, MAHs may be required to write DHCP letter to communicate this information promptly to health care providers involved in prescribing or dispensing of medicines.

The Authority may request MAHs to submit DHCP letters where the Authority believes there is an important safety concern, where the DHCP letter is part of Risk Mitigation Strategy or any other situation that the Authority believes a DHCP letter is needed.

Where an MAHs receives a request from another NRA to submit a DHCP letter, the MAH must notify the Authority and submit DHCP letter provided the product is registered in Botswana. In class effect safety concern, MAHs are expected to collaborate and develop one generic DHCP letter and submit it to the Authority. In cases where an MAH has registered different brands of the same active ingredient in Botswana, MAH is expected to submit a DHCP letter for the locally marketed brand.

MAHs are encouraged to voluntarily submit DHCP letters to the Authority where they believe there is a need to disseminate DHCP letter.

4.8.2 Contents of DHCP letter

A DHCP letter should be clear and concise and contain sufficient detail to meaningfully inform the target audience. The following must be included in the DHCP letter;

a) Purpose of the letter (e.g., to inform prescribers about a specific new drug safety issue)
b) Description of the new information

c) Existing information that has changed, if any (e.g., information that is no longer valid in light of the new information)
d) Action for a health care provider to take in response to the new information, if any

4.8.3 Submission of DHCP letter

MAHs are expected to submit draft DHCP letters to the Authority within 5 working days from the time it's requested.

Where another NRA has requested DHCP letter, the draft should be sent to the Authority when it's sent to the other NRA.

The Authority will review the draft DHCP letter for all submissions and will provide feedback within zf5 working days. Thereafter, the final draft must be submitted to the Authority and circulated within 2 working days**.**
All submissions must be sent through rmu@bomra.co.bw and copy safetyupdates@bomra.co.bw.

4.9 Submission of a Risk Management Plan

4.9.1 Introduction

A pharmaceutical product is authorized on the basis that in the specified indications, at the time of authorization, the benefit risk balance is judged to be positive for the target population. A pharmaceutical product will have multiple risks associated with it and individual risks will vary in terms of severity, effect on individual patients and public health impact. However, not all actual or potential risks will have been identified at the time when an initial authorization is sought and many of the risks associated with the use of a pharmaceutical product will only be discovered and characterized post marketing. Risk Management Plan be submitted following ICH E2E format Guideline (GVP): Module V – Risk management systems.

4.9.2 Objectives

a) Identify or characterize the safety profile of the pharmaceutical product
b) Indicate how to characterize further the safety profile of the pharmaceutical product concerned
c) Document measures to prevent or minimize the risk associated with the pharmaceutical product including an assessment of effectiveness of those interventions.
d) Document post marketing obligations that have been imposed as a condition of the marketing authorization.

To fulfill the above objectives, the RMP should also

a) Describe what is known and not known about the safety profile of the concerned pharmaceutical products
b) Indicate the level of certainty that efficacy shown in clinical trial population will be seen when the medicine is used in the wider target populations seen in everyday medical practice and document the need for studies on efficacy in the post marketing phase (Also known as effectiveness study)
c) Include description of how the effectiveness of risk minimization measurers will be assessed

4.9.3 Contents of the RMP

The risk management plan details the PV activities and risk minimization activities which will be taken to reduce the risk associated with an individual safety concern. RMP should contain the following sections:

a) Pharmaceutical product overview
b) Safety specifications
c) Epidemiology of the indications and target population
d) Non-clinical part of the safety specifications e.g., Toxicity related information
e) Clinical trial exposure
f) Population not studied in the clinical trial
g) Post market experience
h) Identified and potential risks
i) Summary of the safety concerns

4.9.4 Risk minimization activities

The MAH should have the updated SmPC, the labelling, package insert, the pack size, the schedule category as routine risk minimization activities. The MAH should consider when appropriate to have additional risk minimization activities like education materials communication to HCPs etc.

For each safety concern, the following information should be provided:

a) Objectives of the risk minimization
b) Routine risk minimization activities
c) Additional risk minimization activities if any, individual objectives, and justification of why needed
d) How the effectiveness of each risk minimization activities will be evaluated in terms of attainment of their stated objectives
e) What the target is for risk minimization i.e., what are the criteria for judging success, milestones evaluation and reporting.

An RMP update is expected to be submitted at any time when there is a change in the list of the safety concerns, or when there is a new or a significant change in the existing additional pharmacovigilance or additional risk minimisation activities.

4.9.5 Post-authorisation safety study (PASS)

A post-authorization safety study (PASS) is defined as any study relating to an authorised medicinal product conducted with the aim of identifying, characterizing, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures. If an important safety concern, specific to the use of the product in Botswana needs to be investigated the BoMRA may request the Applicant/MAH to conduct a Post-authorisation Safety Study (PASS) or another type of programme capable of ensuring the collection or the relevant safety information. Performing such investigations may be required as a pre-approval commitment of following a local emerging safety issue

A post-authorisation study should be classified as a post-authorisation safety study when the main aim for initiating the study includes any of the following objectives;

a) to quantify potential or identified risks, e.g., to characterise the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population or a population exposed to another medicinal product or class of medicinal products as appropriate, and investigate risk factors, including effect modifiers;
b) to evaluate the risks of a medicinal product used in a patient population for which safety information is limited or missing (e.g., pregnant women, specific age groups, patients with renal or hepatic impairment or other relevant comorbidity or co-medication);
c) to evaluate the risks of a medicinal product after long-term use;
d) to provide evidence about the absence of risks;
e) to assess patterns of drug utilisation that add knowledge regarding the safety of the medicinal product or the effectiveness of a risk management measure (e.g., collection of information on indication, off-label use, dosage, co-medication, or medication errors in clinical practice that may influence safety, as well as studies that provide an estimate of the public health impact of any safety concern);
f) to measure the effectiveness of a risk management measures.

4.9.6 Update of Actions Taken by Other National Drug Regulatory Agencies

MAHs must update BoMRA of all regulatory actions taken by other national drug regulatory authorities which may influence the overall benefit-risk profile of the product and must be communicated to BoMRA as soon as possible but not later than 5 working days after receipt of information. This may include but not limited to the following:

a) Product withdrawal
b) Product recall and product defect
c) Deletion or removal of approved indications by regulatory agencies
d) Failure to renew product registration due to safety reasons
e) Dissemination of Direct Health Professional Communication (DHPC) Letter related to safety issues.
f) Any safety signal of a product as well as any marketing or regulatory decisions taken in the country of origin or other countries where the product is marketed

4.9.7 Safety Variations

Changes to safety aspects of approved labelling information including Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Product Information (PI) must be notified to the Authority. MAHs marketing generics must align their SmPC/PI and PIL with the innovator company's labelling.

The documents should be uploaded in a CD and submitted at BoMRA records unit. The outer cover should be labelled as follows; Name of MAH and Term "Safety Variation or Update". Online submissions must be emailed to records@bomra.co.bw.

The request for the change should be submitted with the underlisted documentation:

a) Covering letter addressed to the Chief Executive Officer of BoMRA
b) Tracked and clean (current and up to date) versions of the document indicating the section where the change(s) have been affected
c) Gap analysis document to indicate changed sections

d) Evidence supporting the need for the change e.g literature
e) Approval letters for the changes from other NRAs if applicable
f) Where the changes to the PI/PIL/SmPC was due to approved variation from BoMRA Department of Product Evaluation and Registration, the applicant should clearly state that and provide variation approval letter as part of the submission.

4.9.8 Minor variation.

Minor variations are changes that may have minimal impact or no impact at all on the overall safety, efficacy, and quality of the medicinal product. The MAH does not need immediate approval from BoMRA to implement changes. They are however expected to have submitted the safety notification within 12 months after implementation.

For a new medicinal product, the MAH is required to submit safety notification to BoMRA immediately after implementation to ensure that there is continuous safety monitoring of the medicinal product.

4.9.9 Major variation

Major variations are changes that could have significant effects on the overall safety, efficacy, and quality of the of the medicinal product. The MAH is required to seek for permission before implementing changes. Where a safety notification is observed, the MAH is required to notify BoMRA within 30 days of being knowledge of the safety concern.

Where an MAH is using the same PI/SmPC, PIL for multiple countries, the MAH is encouraged to make parallel submissions to other NRAs. This will facilitate incorporation of comments from each NRA before finalising the PI/SmPC, PIL.

4.10 Outsourcing of Pharmacovigilance Activities

The MAH may transfer any or all of the pharmacovigilance task and functions, including the role of pharmacovigilance, to another person(s) or organization, but the ultimate responsibility for the fulfilment of all pharmacovigilance obligations and its quality and integrity always resides with the MAH.

5.0 Reliance in Pharmacovigilance

BoMRA will rely on and/or recognize vigilance regulatory decisions and safety concerns from other NRAs and/or trusted institutions/organizations. The following are some of the vigilance regulatory decisions and safety concerns;

1. Safety signals
2. Pharmacovigilance inspection reports
3. Risk minimization plan assessment reports
4. PSUR/PBRERs assessment reports

Annex 1: Submission of ADR and timelines

Type of ICSR	Clinical trials of non-registered product and/or indication	Cases reported for registered products.
Death or Life threatening	As soon as possible, no later than 7 days	As soon as possible, no later than 15 days
Other serious	As soon as possible, no later than 15 days	As soon as possible, no later than 15 days
Non-serious	No expedited reporting Reported in study report	Within 90 days (Following EU-GVP)

Annex 2: Documents Required for PV Inspection

1. Presentation of the Organization of PV activities (overview)
2. Description of Local PV setup
3. Description of QPPV setup and task transfers if any
4. The PV system master file (PSMF)
5. CV of QPPV / PV Focal Person
6. List of products registered in Botswana
7. Number of ADRs submitted
8. Number of PSURs/PBRERs submitted
9. List of RMPs submitted if any