Botswana Medicines Regulatory Authority

BOMRA
MEDICINES REGULATORY AUTHORITY

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1 Contents

Revision status sheet

Page	Changes made	Issue No.	Process owner	Initiated By	Reviewer's name	Date
6	Updated Section 4.1.4 to require MAHs to plan, conduct, monitor and report all relevant PV activities	4.0	Director-Pharmacovigilance And Clinical Trials	Nonofo Thapelo	Nonofo Thapelo/	04/02/2025
9	Section 4.2 was amended to add more guidance on the reporting of suspected ADRs to BoMRA	4.0	Director-Pharmacovigilance And Clinical Trials	Nonofo Thapelo	Nonofo Thapelo/	19/01/2026
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17	Section 4.6 was amended to provide more guidance on the annexure for PSUR submission and submission timelines.	4.0	Director-Pharmacovigilance And Clinical Trials	Nonofo Thapelo	Nonofo Thapelo	19/01/2026
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13	Amended Section 4.4 to introduce the use of a QPPV nominations form	3.0	Director-Pharmacovigilance And Clinical Trials	Nonofo Thapelo	Nonofo Thapelo	07/03/2025
17	Amended Section 4.9 to expand and clarify on the format of RMPs and criteria for submission.	3.0	Director-Pharmacovigilance And Clinical Trials	Nonofo Thapelo	Nonofo Thapelo	07/03/2025
16	Amended Section 4.7 to clarify the criterion for the submission of PSURs	3.0	Director-Pharmacovigilance And Clinical Trials	Nonofo Thapelo	Nonofo Thapelo	07/03/2025
16	4.6 Amended section 4.6 to add the manufacturers and/or MAHs should inform the NRA of any	2.0	Director-Pharmacovigilance And Clinical Trials		Pono Pono	21/09/2023

	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.					
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
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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
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21	5.0 Reliance in Pharmacovigilance added	1.0	Director-Pharmacovigilance and clinical trials		Pono Pono	12/05/2022
8	4.1 Legal provision	3.0	Director-Pharmacovigilance and clinical trials		Pono Pono	03/09/2024
14	4.5 Roles and responsibilities	3.0	Director-Pharmacovigilance and clinical trials		Pono Pono	03/09/2024

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 (Individual Case Safety Reports (ICSRs), Periodic Benefit Risk Evaluation Report (PBRER), risk management plans, product safety labelling variation, emerging safety issues, safety decisions from foreign NRAs.

3 Definitions and abbreviations

3.1 Definition

The following definitions shall apply:

3.1.1 Active Surveillance - A pharmacovigilance system for the collection of case safety information as a continuous pre-organized process. Active surveillance can be:

a. Drug based: identifying adverse events in patients taking certain products;

b. identifying adverse events in certain healthcare settings where they are likely to present for treatment.

c. Event based: identifying adverse events that are likely to be associated with medicinal products, e.g., liver failure.

3.1.2 Adverse Drug Reactions (ADR) -a response to a drug which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

3.1.3 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.

3.1.4 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.

3.1.5 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.

3.1.6 Emerging Safety Issue -a safety issue considered by a marketing authorization 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.

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

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

3.1.9 Market Authorization Holder (MAH)- a Marketing Authorization Holder (MAH) is a company, firm or non-profit organization that has been granted a marketing authorization. This also extends to licensed distributors, legal technical representatives and other designated entities in Botswana.

3.1.10 Medicine- any substance, mixture or combination of substances manufactured, sold or presented for use in -

i. the diagnosis, treatment, alleviation, modification or prevention of disease, illness, abnormal physical or mental condition or the symptoms thereof, or restoring, correcting, or modifying any somatic or psychic or organic condition; or any controlled substance.
ii. a substance or mixture or substances that is used to manufacture medicine or is sold as a raw material, a pre-cursor chemical or intermediate;
iii. any labelled preparation in pharmaceutical dosage form that contains, as active ingredients, one or more substances of natural origin that are derived from plants or animals;
iv. Homeopathic, ayurvedic, or other medicine that contains, as active ingredients, substances of natural origin, and may be derived from any part of plants or animals in a pharmaceutical dosage form;
v. vitamins and minerals prepared in a pharmaceutical dosage form; or
vi. any premix:
vii. investigational medical product.

3.1.11 National Medicines Regulatory Authority (NRA) - Botswana Medicines Regulatory Authority (BoMRA).

3.1.12 National Pharmacovigilance Centre (NPVC) - A pharmacovigilance centre in a country participating in the WHO Program for International Drug Monitoring and is usually a part of or closely linked to the national medicine regulatory authority i.e., BoMRA for Botswana.

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

3.1.14 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.

3.1.15 Safety 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 centre 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 - an 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.

3.1.23 Qualified Person for Pharmacovigilance (QPPV) or Responsible person for Pharmacovigilance- An individual named by the Marketing Authorization Holder (MAH) and approved by the Authority as the person responsible for monitoring of the safety of medical products marketed by the MAH in Botswana.

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 safety 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 must report ADRs to the Authority.

4.1.1 In order to comply with the regulatory pharmacovigilance requirements, the MAH must establish and operate a pharmacovigilance system, with clear and well-defined objectives, to ensure safety monitoring of medicines registered/marketed/exempted in Botswana. The PV system shall be equipped and competent to conduct the planning, monitoring, reporting, analysis of all relevant pharmacovigilance activities. These may include:

a. Continuous Safety Profile Monitoring and Benefit-Risk Evaluation:
    i. MAHs must continuously monitor the safety profiles of registered medicines.
    ii. Conduct benefit-risk evaluations to assess the overall risk associated with the use of medicines.
b. Establishing and Implementing Risk Management Systems:
    i. Develop and implement risk management systems for registered/authorised medicines.
    ii. Evaluate the effectiveness of these systems in minimizing risks associated with medicines.
c. Collection, Processing, and Management of Individual Case Safety Reports (ICSRs):
    i. Collect individual case safety reports from any source (e.g., healthcare professionals, patients).
    ii. Process, manage, and ensure quality control of ICSRs.
    iii. Follow-up for missing information, code, classify, detect duplicates, and evaluate reports.

iv. Ensure timely reporting of ICSRs.

d. Signal Management:
   Implement processes to detect and manage signals related to adverse drug reactions or other safety concerns.
e. Preparation and Submission of Periodic Safety Update Reports (PSURs):
   i. Schedule and prepare PSURs.
   ii. Conduct data evaluation and quality control of PSURs.
   iii. Submit PSURs to BoMRA and assess their findings.
f. Meeting Commitments and Responding to Authority Requests:
   i. Fulfil commitments related to pharmacovigilance activities.
   ii. Provide correct and complete information as requested by regulatory authority.
g. Integration with Product Quality Defect Systems:
   Ensure interaction between pharmacovigilance and product quality defect reporting systems.
h. Communication About Safety Concerns:
   i. Notify the regulatory authority of changes to the risk-benefit balance of medicines.
   ii. Communicate safety concerns effectively to the regulatory authority.
   iii. Crises prevention and management
i. Communication to Patients and Healthcare Professionals:
   i. Inform patients and healthcare professionals about changes to the risk-benefit balance of medicines.
   ii. Aim to ensure safe and effective use of medicines through communication.
j. Safety variations:
   i. Update product information with current scientific knowledge.
   ii. Incorporate conclusions and recommendations from regulatory authorities' assessments.
k. Implementation of Variations to Marketing Authorizations:
   i. Implement variations to marketing authorizations for safety reasons.
   ii. Adhere to urgent requirements for necessary changes.

These processes ensure that MAHs maintain a robust pharmacovigilance system that meets regulatory standards in Botswana, promoting the safety and effectiveness of medicines in the market.

4.2 ADR Reporting Timelines by MAHs to BoMRA

a) The MAH is required to report all suspected adverse events that were detected in Botswana. Cases eligible for reporting include;
   i. Known and unknown adverse events
   ii. Serious, mild, non-serious adverse events
   iii. Local and system adverse events
   iv. Medication Errors
   v. Lack of Efficacy including anti-microbial resistance
   vi. Abuse, misuse of medication
   vii. Off-label use
   viii. Other special situation reports detected in Botswana

b) 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.

c) For the reporting and management of serious, cluster and non-serious adverse events following immunization, MAHs shall refer to the National Guidelines for Adverse Events Following Immunisation (AEFI) (**BOMRA/PCT/PV/P07/G01**)

d) 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 as per to ICH E2A and E2D Guidelines:

e) ICSR Submission timelines

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 Authority. 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. Guidance on reporting means and timelines can be found in Botswana Good Clinical Practice Guideline (**BOMRA/PCT/CT/P01/G01**).

4.2.4 Requirements for adverse events reporting by MAH

a) 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 I for reporting timelines).
b) All reports shall meet the minimum requirements for a valid ICSR report with; an identifiable patient, an identifiable reporter, a suspected drug and a suspected adverse event.
c) The MAH shall also submit additional information obtained following the implementation of follow-up activities for the adverse event received which may include investigations of serious and cluster adverse event.

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 and such system shall be implemented in Botswana. This is a way the company demonstrates that it accepts responsibility and liability for its products on the market and their safe use. The pharmacovigilance system shall be equipped to be able to plan, conduct, monitor and report all relevant PV activities.

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 in Botswana 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 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. 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 minimization and prevention and those appropriate measures are taken by the marketing authorization 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 authorization 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 authorization holder with BoMRA, including communication on new or changed risks, the pharmacovigilance system master file, risk management systems, risk minimization measures, periodic safety update reports, corrective and preventive actions, and post-authorization safety studies.
f) the update of product information by the marketing authorization 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 for 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 and include:

a) continuous safety profile monitoring and benefit-risk evaluation of authorized medicinal products.
b) establishing, assessing, and implementing risk management systems and evaluating the effectiveness of risk minimization.
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 authorization 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 authorizations for safety reasons according to the urgency required.

4.3.10 Pharmacovigilance System Master File

Every MAH shall have Pharmacovigilance System Master File 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

The marketing authorization holder who has registered medicinal products in Botswana must have permanently and continuously at its disposal a QPPV. The QPPV is responsible for the establishment and maintenance of the local pharmacovigilance system.

4.4.1 The QPPV shall be based in Botswana. However, where not practically possible, the MAH must have a LTR or Pharmacovigilance officer who resides in Botswana and as such have a QPPV based in SADC region who should be easily accessible to the LTR or Pharmacovigilance officer.

4.4.2 The QPPV and/or the LTR should have acquired adequate theoretical and practical knowledge for the performance of pharmacovigilance activities. The QPPV and or LTR must be a healthcare professional with Medicine, Pharmacy, Nursing or any other healthcare professional degree recognized by the Authority. They 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.

4.4.3 The MAH must provide the BoMRA with the details of the QPPV the LTR within 7 days of appointment (including full name, postal address, email address, telephone, and fax numbers). Using the Notification Form for Designation as a Qualified Person for Pharmacovigilance (QPPV)-(***BOMRA/PCT/PV/P01/G02/F02***), Job Description and Curriculum Vitae. Any changes of these details should be communicated to the Authority within 7 working days of implementation.

4.4.4 Back-up procedures in the case of absence of the QPPV/LTR should be in place and should be accessible through the QPPV/LTR contact details. The QPPV/LTR should ensure that the back-up person has all necessary information to fulfil the role. The Back-up QPPV/LTR shall meet all the requirements of a QPPV/local Pharmacovigilance Officer. The Back-up QPPV/ local Pharmacovigilance Officer shall however receive training in pharmacovigilance appropriate for his/her roles.

4.4.5 Roles and responsibilities

The roles and responsibilities of the QPPV and/or LTR should include.

a) having an overview of medicinal product safety profiles and any emerging safety concerns.
b) having awareness of any conditions or obligations adopted as part of the marketing authorizations and other commitments relating to safety or the safe use of the products.
c) having awareness of risk minimization measures.
d) being aware of and having sufficient authority over the content of risk management plans and their implementation in Botswana.
e) being involved in the review and sign-off of protocols of post-authorization safety studies conducted in Botswana or pursuant to a risk management plan agreed upon in Botswana.
f) having awareness of post-authorization safety studies requested by a competent authority including the results of such studies.
g) ensuring the conduct of pharmacovigilance and submission of all pharmacovigilance-related documents in accordance with the legal requirements and GVP.

h) ensuring the necessary quality, including the correctness and completeness, of pharmacovigilance data submitted to BoMRA.
i) ensuring a full and prompt response to any request from BoMRA for the provision of additional information necessary for the benefit-risk evaluation of a medicinal product.
j) providing any other information relevant to the benefit-risk evaluation to BoMRA.
k) providing input into the preparation of regulatory action in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and communication to patients and healthcare professionals).
l) act as a contact point for pharmacovigilance inspections.

4.5 Signal Management

i. The Authority mandates MAHs to routinely conduct signal detection through review of ICSRs, scientific literature and any other appropriate sources of data.
ii. MAHs are the expected to conduct signal validation and assessment and if the signal has been confirmed, they are required to inform BoMRA within 30 calendar days if the next PSUR submission date is more than 6 months away from date of conclusion of assessment, else the MAH shall include the detailed assessment in the next PSUR.
iii. Authority will conduct its own signal detection, validation and assessment processes and will communicate any confirmed signals and the recommended regulatory actions where necessary. If deemed necessary, the Authority may require MAHs to evaluate any suspected significant safety concerns and subject them to an investigation as per the signal management process. In such a situation the MAH will be required to submit the analysis report within 30 calendar days of receiving the notification.

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

a) 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.

b) 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. A pharmacovigilance plan for the product in line with its risk management plan where applicable, is also to be submitted.

c) After registration of the product in Botswana, PSURs/PBRERs should be submitted to BoMRA at defined time intervals with specific national annexure The annexure shall include information on the cumulative exposure for Botswana and the African Region as a whole, ICSRs identified, signals, safety concerns, and other product safety and quality issues identified in Botswana may affect the benefit-risk balance of the product.

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 the 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 literature including academic conferences).
e) Updated Summary of product characteristics or product information, patient information leaflet and company core data sheet.
f) All PSURS/PBRER shall be submitted through the BoMRA Regulatory Information Management System (BRIMS). The MAH is required to create an account on the BRIMS platform at brims.bomra.co.bw/#/public/login to be able to submit their PSUR/PBRER and access other BoMRA services. The PSURs or PBRERs should be clearly labelled; Name of MAH and Term "PSURs or PBRERs".

4.6.1 Timelines for PSUR and PBRERs Submission

a) Submission of PSUR/PBRERs is required for newly registered molecules/active pharmaceutical products and biologicals/vaccines in Botswana. If the newly registered molecules/active pharmaceutical products and biologicals/vaccines is newly approved internationally and locally, the submission should be every 6 months for the first 2 years after approval and later annually for the next two years and thereafter, each time during product marketing authorization renewal.

b) Furthermore, if the new molecule/active pharmaceutical product and biological/vaccine has been registered and marketed in a country regulated by a stringent Authority for 5 years or more, the MAH should submit a PSUR/PBRER annually for the first three years, from time of registration in Botswana, and thereafter at the time of product marketing authorization renewal.

c) For generics and medicinal products registered for 10 years or more in Botswana, their PSURs/PBRERs must be submitted at the time of product marketing authorization renewal. Submissions will be mandatory for innovator brands upon renewal of registration while generic producers may be required to submit a PSUR/PBRER in the case where their brand is the first or lead product in the Botswana market or by request from the Authority.

d) Where a significant safety concern arises, the Authority reserves the right to request any MAHs to submit a PSUR/PBRER at any time including the intervals between the marketing authorization renewals. The MAH is required to fulfil such requests and submit the PSUR/PBRER within 90 calendar days of receiving the notification, unless otherwise specified.
e) PSURs shall be submitted within the following timelines:
    i. within 70 calendar days of the data lock point (day 0) for PSURs covering intervals up to 12 months (including intervals of exactly 12 months); and

ii. within 90 calendar days of the data lock point (day 0) for PSURs covering intervals in excess of 12 months;

f) Submission of PBRERs/PSURs may be aligned with global submission or the EURD submission timeline in consultation and consensus with BoMRA. In the spirit of reliance, once the MAH has sought such an approval from BoMRA, the MAH shall ensure that each submission is accompanied by the public assessment report from EMA. and an indication of consideration of any Botswana or regional specific safety concerns that may appear in the Botswana Annexure.

g) Where applicable, the Authority will provide feedback within 90 working days after the submission of PSUR/PBRER.

4.7 Safety Communication

New or updated information about medicinal products emerges throughout its product's life cycle. As a result, MAHs may be required to communicate this information promptly to health care providers, patients, communities or any other relevant stakeholders. Communications may also be issued as part of a product's risk minimization measures. Examples of communication that may be issued may include:

a) Dear Healthcare Professional Letters
b) Communiques as part of RMP Communications as part of crisis prevention and management
c) Other forms of communications as developed in agreement with BoMRA e.g product recall letters, supply chain issues etc.

All safety related communications to be disseminated by the MAH shall receive approval and authorization from BoMRA. Applications for such approval shall clearly indicate the target audience, medium of communication and means of measuring the effectiveness to ensure that the message reaches the appropriate audience and is well understood.

4.7.1 Dear Healthcare Professional Letter and its Contents

4.7.1.1. The MAH may voluntarily develop a DHCP letter or as 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.

4.7.1.2. 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.

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

4.7.2 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.

4.7.3 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 5 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.

4.8 Submission of a Risk Management Plan

4.8.1 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. A Risk Management Plan should be submitted following the ICH E2E format Guideline (GVP): Module V – Risk management systems. Each submission shall be accompanied by a Botswana specific annexure as per the format in **Botswana Specific Annex for Risk Management Plans (*BOMRA/PCT/PV/P01/G02/F01*)**.

The RMP shall be submitted for the following scenarios:

a) Upon registration of a new molecule/active pharmaceutical ingredient.
b) Upon registration of biologicals products and/or vaccines

Upon renewal of registration as part of the updated common technical document (CTD)

c) In case of any new safety concern, signal, or significant safety finding identified in Botswana and other territories. submitted within 30 calendar days of the effective date of the revised RMP.

The Authority reserves the right to request the submission of a Risk Management Plan (RMP) if a safety concern or signal related to the product is identified in other territories where the product is registered. Upon receipt of such a request, the MAH shall submit the RMP to the Authority within 30 calendar days.

4.8.2 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 fulfil 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.

4.8.3 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-Authorisation experience
h) Identified and potential risks
i) Summary of the safety concerns
j) Pharmacovigilance Plan
k) Risk Minimization Measures and a Summary of the Risk Management Plan

4.8.4 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 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.

4.10 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 and its analysis thereof 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.

4.11 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 rmuservices@bomra.co.bw and copy safetyupdates@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.

For classification of variations, BoMRA has adopted the European Medicines Agency classification system as outlined in the latest applicable version of **EMA Guideline on Variations**, wherein the variations will be classified as follows:

4.11.1 Minor variation.

Type 1A variations, colloquially, referred to as 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 of 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.

4.11.2 Major variation

Type 1B and Type II variations will be referred to, collectively, as major variations. These 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 such 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.

4.12 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.

4.13 Reliance in Pharmacovigilance

BoMRA may 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;

a. Safety signals
b. Pharmacovigilance inspection reports
c. Risk minimization plan assessment reports
d. PSUR/PBRERs assessment reports

5 References

1. Medicines and Related Substances Act
2. Medicines and Related Substances Regulations
3. EU Good Vigilance Practices Guidelines
4. ICH Guidelines (PSUR, RMP, ICSR Management)