Botswana Medicines Regulatory Authority

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Table of Contents

Revision status sheet

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1 Purpose

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

2 Scope

The scope of this guideline includes pharmacovigilance activities for approved medicines in post-authorisation phase in Botswana. Matters under scope include: a) The organisation of the pharmacovigilance system and the management of outsourced activities, b) The reporting of safety information (ICSRs, PBRER, emerging safety issues, safety decisions from foreign NRAs), c) Risk management planning, d) Post-authorisation studies and e) 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 or Experience - Adverse Event - 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 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 Authorisation 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 Programme 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) 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.

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.

3.2 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. Method

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 7 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 by the pharmacovigilance officer, BoMRA quoting the number assigned to the case report within five working days. 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 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 pharmaceutical company 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 pharmaceutical company 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 authorised representative shall be provided in the promotional material to report ADRs.

4.3 Pharmacovigilance system for MAHs

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.

PV system at MAH should at least consist of the following: -

a. Product safety data and Individual ADR 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.

The MAH holder should be capable of providing within 7 business days the pharmacovigilance system master file intended for submission to BoMRA.

4.4 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 MAH 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.

4.4.1 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 to take regulatory action wherever considered necessary, based on the result of the inspection.

4.4.2 Inspection Procedure

4.4.2.1 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.

4.4.2.2 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

4.4.2.3 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. When necessary the inspectors may also request other documents related information. They shall also conduct interviews of the relevant persons, other than QPPVs, involved in different PV activities.

4.4.2.4 Inspection findings
Each inspection will result in an inspection report and the findings shall be classified into critical, major and minor. The report will be made available to the PV department of MAH.

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.

4.4.2.5 Inspection follow up
The following follow up actions should be considered as appropriate

- Review of the MAH CAPA plan
- Review of the periodic progress when deemed necessary
- Request for submission of previously un submitted data, submission of variations
- Request for issuing safety communications including amendments of marketing and or advertising information

- Communication of the findings to other regulatory authorities
- Regulatory actions

4.4.2.6 In the event of non-compliance

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

- Updating of package inserts /SMPC
- Product recalls
- Suspension/cancellation /withdrawal of marketing authorization
- Restriction on approvals of new marketing authorization applications

4.5 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.

4.6 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.

PSURs/PBRERs are reports that reflect the changes in safety, quality and effectiveness profile of the product are to be submitted to the 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).

4.7 Timelines for PSUR AND PBRERs Submission

Submission of PSUR/PBRERs for products registered in Botswana should be submitted 6 monthly 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. However, MAH may be notified by BoMRA to submit 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.

4.8 Dear Healthcare Professional Letters and alert notices

Pharmaceutical industry may be required to write dear healthcare professional letters (DHCP) and/or alert notices, including update of the patient information leaflet depending on the nature of the medicine safety issue/s observed or product defect and/or recall. A copy of the DHCP letter to be sent to HCPs (Healthcare professionals) should be submitted to BoMRA for approval 5 working days prior to distribution.

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

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

To fulfill the above objectives, the RMP should also

- Describe what is known and not known about the safety profile of the concerned pharmaceutical products
- 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)
- 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) Nonclinical 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

Regulatory actions taken by other national drug regulatory authorities which may influence the overall benefit-risk profile of the product 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.

4.9.7 Safety Update/ Notifications

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 supervision of the medicinal product.

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.

4.9.8 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 .

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. CV of QPPV / PV Focal Person
5. List of products registered in Botswana
6. No of ADRs submitted
7. No of PSURs/PBRERs submitted
8. List of RMPs submitted if any