Medicines Control Authority of Zimbabwe

MCAZ/PVCT/GL-02

PHARMACOVIGILANCE GUIDELINE FOR PHARMACEUTICAL INDUSTRY

EFFECTIVE DATE: 25/2/2022

Medicines Control Authority of Zimbabwe

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Authorised for use by: Director-General	..... Signature	25/2/2022 ..... Date

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1.0 APPLICATION

This guideline was developed by the Medicines Control Authority of Zimbabwe to provide guidance and information to all Market Authorisation holders, Principals, Applicants, Manufacturers and Local Representatives of registered products to help in the continuous safety monitoring of products granted marketing authorization or registered in Zimbabwe. The guidelines apply to all registered medicinal products in Zimbabwe and does not cover for reporting of ADRs by manufacturers or MAH. For ADR reporting please refer to the Zimbabwe Pharmacovigilance Policy Handbook and latest version of Pharmacovigilance Electronic Reporting System User Manual.

2.0 PURPOSE

This guideline is in line with the Authority's mandate to ensure accessible medicines are safe and of good quality. To determine that Marketing Authorisation Holders comply with pharmacovigilance obligations.

3.0 BACKGROUND AND INTRODUCTION

Manufacturers and/or MAHs are required to set up a vigilance system of their medicinal products and periodically report vigilance data to the Authority.

Medicinal products are approved based on clinical trials data available at the time and in most cases on several hundreds or thousands patients. The limited number of patients included in clinical trials, the exclusion of certain patients at-risk, the lack of significant long-term treatment experience and the limitation of concomitant therapies do not allow a thorough evaluation of the safety profile. Under such circumstances, the detection or confirmation of rare adverse reactions is particularly difficult, if not impossible. The risk benefit balance for a product may also change from time to time hence the need for safety monitoring.

These guidelines therefore provide the requirements for the safety monitoring during the life cycle of registered medicinal products and communication of safety information related to these products.

The guidelines contain the requirements for post approval safety monitoring of registered products, including the requirements for the following:

3.1 Periodic Safety Updates Reports (PSUR) and Periodic Benefit Risk Evaluation Reports (PBRER)
3.2 Risk Management Plan (RMP)
3.3 Post Authorization Safety Studies (PASS)
3.4 Post Authorization Efficacy Studies (PAES)
3.5 Safety Variations
3.6 Safety Communication
3.7 Change of category for distribution.

4.0 DEFINITIONS

4.1 **Adverse Drug Reaction (ADR) / Adverse Reaction (AR):** 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.

4.2 **Adverse Event or Adverse Experience (AE):** Adverse event/experience is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product that may present during treatment with a medicine, but which does not necessarily have a causal relationship with this treatment.

4.3 **Adverse Events Following Immunization (AEFI):** Adverse Event Following Immunization is any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

4.4 **Authority** means Medicines Control Authority of Zimbabwe.

4.5 **'Dear Healthcare Professional (DHCP) Letter':** A 'Dear Healthcare Professional Letter' is a correspondence usually in the form of a mass mailing from the Marketing Authorization Holder (MAH), the Local Representative or the Authority addressed to doctors, pharmacists, nurses and other healthcare professionals regarding important new information. The DHCP letters are intended to inform the recipients of the need to take certain actions or adopt their practices to minimize particular risks and/or to reduce burden of adverse drug reactions with a medicinal product.

4.6 **Drug Abuse:** Drug abuse is a persistent or sporadic, intentional excessive use of medicines, which is accompanied by harmful physical or psychological effects.

4.7 **Identified risk:** An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. An important identified risk is an identified risk that could have an impact on the benefit-risk of the product or have implications for public health. What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk and the impact on public health. Normally any risk that is likely to be included in the contraindications or precautions section of the product information should be considered important.

4.8 **Local Representative:** The company or legal entity that represents the Applicant in Zimbabwe and performs functions delegated by the Applicant.

4.9 **Applicant:** The company or legal entity in whose name the marketing authorization for a product has been granted and is responsible for all aspects of the product and compliance with the conditions of marketing authorization.

4.10 **Medicinal product/ Drug:** A substance or mixture of substances prepared, sold or represented for use in:

4.10.1 the diagnosis, treatment, mitigation or prevention of disease, disorder of abnormal physical state or the symptoms of it, in man or animal, or

4.10.2 restoring, correcting, or modifying organic functions in man or animal.

4.11 **Missing information:** Information about the safety of a medicinal product which is not available at the time of submission of a particular risk management plan and

which represents a limitation of the safety data with respect to predicting the safety of the product in the marketplace. Examples of missing information include populations not studied (e.g. pregnant women or patients with severe renal impairment) or where there is a high likelihood of off-label use.

4.12 **New Chemical Entity:** A chemical or biologically Active Pharmaceutical Ingredient (API) that has not previously been registered as an ingredient of any pharmaceutical product.

4.13 **Off Label Use:** Off label use of a medicine is use for indication, dosage form, dose regimen, population or other use parameter not mentioned in the approved labelling of the medicinal product.

4.14 **Periodic Benefit Risk Evaluation Report (PBRER):** An update of the world-wide marketing experience of a medicinal product at defined times with focus on formal evaluation of benefit in special population at defined times during post registration period.

4.15 **Periodic Safety Update Report (PSUR):** A Periodic Safety Update Report (PSUR) is intended to provide an update of the worldwide safety experience of a medicinal product to the Authority at defined time points post authorization. At these times, Marketing Authorization Holders are expected to provide succinct summary information together with a critical evaluation of the benefit-risk balance of the product in the light of new or changing information.

4.16 **Pharmacovigilance:** Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug -related problem.

4.17 **Post-Authorization Efficacy Study (PAES):** A study which is performed after the marketing authorization and is aimed principally to further evaluate the efficacy of the medicinal product.

4.18 **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.

4.19 **Potential Risk:** An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed. An example is toxicological findings seen in non-clinical safety studies which have not been observed or resolved in clinical studies. An important potential risk is a potential risk that could have an impact on the benefit-risk of the product or have implications for public health. What constitutes an import risk will depend upon several factors, including the impact on the individual, the seriousness of the risk and the impact on public health. Normally any risk that is likely to be included in the contraindications or precautions section of the product information should be considered important.

4.20 **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 the products marketed by the MAH in Zimbabwe.

4.21 **Risk Management Plan:** A detailed description of the risk management system. The Risk Management Plan may be submitted as part of the dossier that is evaluated by the Authority before a medicine can be authorized and which is regularly

updated as new information becomes available. Risk Management Plans include information on a medicine's safety profile and explain the measures that are taken in order to prevent or minimize the risks of medicine in patients.

4.22 Risk Minimization Measure or Activity: An intervention intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a medicine or to reduce its severity should it occur.

4.23 Risk Management System: A set of Pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions.

4.24 Safety Concern: An important identified risk, important potential risk or important missing information.

4.25 Serious Adverse Drug Reaction or Serious Adverse Event: An adverse reaction or event which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defects.

4.26 Spontaneous Report or Spontaneous Notification of Adverse Reactions/Events: A communication to a company, regulatory authority or an organization that describes a suspected adverse event/reaction in a patient who is given one or more medicines, and which is not derived from a study.

4.27 Target Population: The patients who might be treated with the medicinal product in accordance with the indication(s) and contraindications in the authorized product information.

4.28 Unexpected Adverse Reaction: An unexpected adverse reaction is one in which the nature, specificity, severity and outcome is not consistent with the applicable product information (i.e., with the approved package inserts for registered medicines, or the investigator's brochure or other product information for unregistered medicines

5.0 GUIDELINES

5.1 Periodic Safety Updates Reports (PSUR) and Periodic Benefit Risk Evaluation Reports (PBRER)

Periodic safety update reports (PSURs) are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product for submission by applicants at defined time points during the post-authorisation phase. Periodic Benefit Risk Evaluation Reports (PBRERs) are pharmacovigilance documents which provide an update of the world-wide marketing experience of a medicinal product at defined times with focus on formal evaluation of benefit in special population at defined times during post registration period. PSURs/PBRERs should ONLY be submitted for medicinal products registered in Zimbabwe and which have been given that condition at market authorisation or post registration as deemed necessary by the Authority.

The main objective of a PSUR is to present a comprehensive, concise, and critical emerging information in the context of cumulative information on benefits and risks. The PSUR is a tool for post- authorisation evaluation in the lifecycle of a

product. While PSUR and PBRER may be used interchangeably in this guideline, it must be understood that these documents are different. Whilst, the primary objective of the PSUR is to provide a comprehensive picture of the safety of approved medicinal products with recognition that the assessment of the risk of a medicinal product is most meaningful when considered in light of its benefits, the PRBER provides a greater emphasis on benefit than the PSUR, particularly when risk estimates change importantly. For additional information on the differences between the PSUR and PBRER reference is made to ICH E2C and ICH E2C (R2) Guidelines respectively.

5.1.1 Objectives of PSUR/PBRER

PSUR/PBRER presents the worldwide safety experience of a medicinal product at defined times post authorization, in order to:

5.1.1.1 Report all the relevant new information from appropriate sources;
5.1.1.2 Relate these data to patient exposure;
5.1.1.3 Summarize the market authorization status in different countries and any significant variations related to safety;
5.1.1.4 Create periodically the opportunity for an overall safety re-evaluation;
5.1.1.5 Provide a formal and concise evaluation of benefit unless the safety or benefit-risk profile has changed significantly during the reporting interval.
5.1.1.6Indicate whether changes should be made to product information to optimize the use of the product.

5.1.2 Frequency of review and Submission

5.1.2.1 PSURs/PBRERs are generally NOT requested routinely**.** Please note that PSURs/PBRER shall be submitted **ONLY** when this is given as a condition in the marketing authorisation of the product or at any point post authorisation when requested by the Authority based on safety concerns or when the Authority deems it necessary. This condition will be communicated to the applicant or MAH. Not all products are given this condition. A risk based approach is used to determine whether submission of PBRER or PSUR should be a condition for registration of the product..

5.1.2.2 When given as a condition of registration or when requested by the Authority, PSURs/PBRERs should be submitted as stated below unless otherwise specified by the authority.

i. Every 6 months for the first two years, yearly for the following 2 years, and at 3-year intervals thereafter.
ii. When requested by the Authority, PSURs/PBRERs must be submitted within 30 calendar days of the request.

5.1.2.3 Other details will be communicated by the Authority on a case-by-case basis. The Authority will provide feedback on any PSUR or PBRER submission within sixty (60) working days.

PSURs and PBRERs should be harmonized with the International Birth Date of the Product. Generally, each PSUR and PBRER should cover the period of time since the last PSUR/PBRER and should be submitted within 60 days after the Data Lock Point. Presentation of the information contained in the PSUR and PBRER shall be in the format recommended by ICH E2C and ICH E2CR2 Guidelines respectively.

Please note that the Authority employs reliance model therefore for PSURs/PBRERs which are also submitted to reference stringent regulatory agencies such as EMA and others, summarised assessment reports and or feedback reports/responses or correspondences concerning the PSUR/PBRER from such agencies should be submitted to the Authority and in such cases full reports for PSUR.PBRER should not be submitted.

For medicinal products with marketing authorization in different countries, the MAH may synchronize the Local Birth Date (LBD) with the International Birth Date (IBD). The Authority will accept a single harmonized IBD and Data Lock Point (DLP) for each product in order to reduce the burden of work in preparing PSURs/PBRERs for different regulatory authorities.

In situations where a MAH is preparing PSURs/PBRERs on annual basis or longer period for different regulatory authorities based on the IBD and the Authority requires a six-month cycle based on the LBD, the most recent PSUR/PBRER with a longer time frame will be acceptable to the Authority.

The Authority may also request for Ad hoc PSUR/ PBRERs i.e., reports outside the specified reporting requirements when there are new risks, when risks have changed, when efficacy/effectiveness has changed, or when there are changes to the benefit-risk profile of a medicinal product.

5.2 Risk management plan (RMP)

Medicinal products are authorised on the basis that for the specified indication(s), at the time of authorisation, the risk-benefit balance is judged to be positive for the target population. With the understanding that some adverse drug reactions will only be discovered and characterised in the post-authorisation phase, it is therefore imperative for a risk management system to be documented which allows for identification, characterisation and minimisation of a medicinal product's important risks. In relation to risk management of medicinal products, Applicants are responsible for:

i. Ensuring that the RMP constantly monitors the risks of its medicinal products issued with marketing authorization in compliance with relevant legislation and reports the results of this, as required, to the Authority;

ii. Taking all appropriate actions to minimize the risks of the medicinal product and maximize the benefits including ensuring the accuracy of all information produced by the company in relation to its medicinal products, and actively updating and promptly communicating it when new information becomes available.

5.2.2 Objectives of a RMP

5.2.2.1 The overall aim of risk management is to ensure that the benefits of a particular medicinal product (or a series of medicinal products) exceed the risks by the greatest achievable margin for the individual patient and for the target population.

5.2.2.2 RMPs are to provide the measures to be taken to prevent or minimize the medicine's risks in patients post authorization. This involves detailing the known safety concerns with the medicine and how they can be managed. It also includes details of any additional studies that have been recommended at the time of authorisation to provide more information on the medicine's safety profile.

5.2.3 Requirements of a RMP

The RMP must contain the following elements which:

5.2.3.1 Identify or characterize the safety profile of the medicinal product(s) concerned;
5.2.3.2 Indicate how to characterize further the safety profile of the medicinal product(s) concerned;
5.2.3.3 Document measures to prevent or minimize the risks associated with the medicinal product including an assessment of the effectiveness of those interventions;
5.2.3.4 Document post-authorization obligations that have been imposed as a condition of the marketing authorization.
5.2.3.5 Describe what is known and not known about the safety profile of the concerned medicinal product(s);
5.2.3.6 Indicate the level of certainty that efficacy shown in clinical trial populations 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-authorization phase (also known as effectiveness studies);
5.2.3.7 Include a description of how the effectiveness of risk minimization measures will be assessed.

5.2.4 Conditions for Submission

5.2.4.1 Risk management plans are generally NOT requested.

5.2.4.2 Please note that a risk management plan shall be submitted **ONLY** when this is given as a condition at the marketing authorisation of

the product or at any point post authorisation when requested by the Authority on the basis of safety concerns or when the Authority deems it necessary. This condition will be communicated to the applicant or MAH. A risk-based approach is used to determine whether submission of a risk management plan should be a condition for registration of the product.

RMP submission should occur within 90 days from the date of request, or as specified by the Authority. A risk-based approach is used to determine whether submission of a risk management plan should be a condition for registration of the product.

5.2.5 Structure of the RMP

5.2.5.1 The structure and format of the RMP should be in-line with the EMA GVP Module V – Risk management systems.

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf

5.2.6 Zimbabwe Specific Annex to the global or EU-RMP

5.2.6.1 The Authority recommends that where an existing global or EU-RMP is submitted, a summarised Zimbabwean Specific Annex should be included to the global or EU-RMP.

5.2.6.2 A Zimbabwe Specific Annex is required whenever there are differences between the Zimbabwean implementation of the RMP and what is proposed in the global or EU-RMP.

5.2.6.3 The Zimbabwe Specific Annex should identify any differences between the global/ EU-RMP and the local implementation of risk management activities, for example: any differences between the risk minimization activities undertaken as reflected in the content of the EU Summary of Product Characteristics (SmPC) and the proposed local Product Information (PI), and the reasons for the difference. This will allow the Authority to assess the appropriateness of the proposed RMP in the Zimbabwe environment.

5.2.7 Purpose of the Zimbabwe Specific Annex

5.2.7.1 The Zimbabwe Specific Annex should provide local specific information that is important in assessing the 'risk' in the population (and therefore appropriateness of proposed plans/activities), the relevance of pharmacovigilance and risk management activities

locally, and identify and explain the reasons for any differences with activities planned globally or in the EU.

5.2.8 Content of Zimbabwe Specific Annex

This should include:

5.2.8.1 Differences in indications between the European Union (EU) and Zimbabwe if applicable.
5.2.8.2 Zimbabwe specific epidemiological information on the population to be treated if available (information relating to the size of the target population or any specifics that is needed to assess the safety of the use of the product in the local population).
5.2.8.3 Local information if available, on potential for medication errors or other risks.
5.2.8.4 Applicability of EU activities to the local environment if no specific Zimbabwean data will be collected.

Insert 1 below is a recommended format for the Zimbabwe Specific Annex

1. **Introduction - Purpose of the Zimbabwe Specific Annex**
2. **Pharmacovigilance practice - Routine pharmacovigilance systems in Zimbabwe and studies referenced in the RMP**
3. **Describe involvement of Zimbabwe and applicability of global studies to the local environment, or—if not applicable or relevant to the local environment—include a justification.**
4. **Risk minimization plan - Address how risk minimization activities will be implemented and evaluated in Zimbabwe. If surveys or studies are referenced in the Zimbabwe Specific Annex, copies of outlines and protocols should be provided.**
5. **Justification (if applicable) - Provide a justification of activities in the EU that are not to be implemented in Zimbabwe. Indicate how and when evaluation of risk minimization activities, including educational activities, will be undertaken. Applicants are responsible for showing that the measures they are using to mitigate risk are working and, if not, what actions they will take to ensure effectiveness.**
6. **Contact person for RMP-This is the person the Applicant considers responsible for the implementation of the RMP activities in Zimbabwe**

Insert 1: Recommended format for the Zimbabwe Specific Annex

All RMPs submitted shall be accompanied by a declaration signed by the Applicant. The declaration should indicate that the Applicant has read the RMP and will ensure implementation of all activities outlined in the RMP.

5.3 Post-Authorisation safety study (PASS)

Post-Authorisation safety study is initiated, managed, or financed by the applicant as well as those conducted by a third party on behalf of the applicant, or conducted upon request by the Authority. This guidance should be used for all PASS studies.

5.3.1 Objectives of PASS

PASS is conducted with the following objectives;

5.3.1.1 Quantify potential or identified risks, e.g. to characterize the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population or a population exposed to another drug or class of drugs, and investigate risk factors and effect modifiers;

5.3.1.2 Evaluate risks of a medicinal product used in patient populations for which safety information is limited or missing (e.g. special populations - pregnant women, specific age groups, patients with renal or hepatic impairment);

5.3.1.3 Assess patterns of drug utilization that add knowledge on the safety of the medicinal product (e.g. indication, dosage, co-medication, medication errors);

5.3.1.4 Measure the effectiveness of a risk minimization activity

5.3.1.5 Evaluate the risks of a medicinal product after long-term use
Provide evidence about the absence of risks.

5.3.1.6 This guidance applies to studies that involve primary collection of safety data directly from patients and health care professionals and those that make secondary use of data previously collected from patients and health care professionals for another purpose.

5.3.2 When a PASS may be conducted

Post-Authorisation safety study may be requested by the Authority and conducted by the applicant under the following conditions:

5.3.2.1 As a condition to the granting of the marketing authorization, or after the granting of a marketing authorization if there are concerns about the risks of the authorized medicinal product affecting the population of Zimbabwe which needs further identification and characterization of the risks.

5.3.2.2 As part of a marketing authorization granted under exceptional circumstances.

5.3.2.3 Required in the risk management plan to investigate a safety concern or evaluate the effectiveness of risk minimization activities.

5.3.2.4 PASS conducted voluntarily by the applicant.

The study protocol for Post Authorization Studies should be approved by the relevant Ethics Committees such as MRCZ and the Authority. The study should be conducted in line with MASCA and its regulation, Clinical trial application guidelines and the Guidelines for Good Clinical Practice in Zimbabwe.

5.3.3 Study population

The study should be conducted in a Zimbabwean population or in a study population to be determined in consultation with the Authority.

5.3.4 Study Design

The study design will be submitted in the protocol for the PASS study and pharmacoepidemiologic study designs may be adopted depending on the objectives of such studies.

5.3.5 Roles and Responsibilities

Applicant

5.3.5.1 The Applicant shall bear sole responsibility for all regulatory and technical aspects of the PASS.

5.3.5.2 The Applicant shall develop the study protocol following the prescribed format by the Authority.

5.3.5.3 The Applicant shall ensure that the PASS study does not commence before the protocol for the study is approved by the Authority.

5.3.5.4 All protocol amendments during the study shall be submitted to the Authority for approval before such amendments are carried out, however, where such amendments are needed to protect the safety of patients, this may be carried out and the Authority informed immediately by phone call, followed by a written report within 48 hours.

5.3.5.5 The applicant shall submit annual study progress reports to the Authority specifying the status of the study and information on participants including but not limited to the date enrolment began, number enrolled, number withdrawn from the study and reasons for withdrawal and expected date of completion of the study. The applicant shall submit a final study report to the Authority not later than 90 days after completion of the study.

The Authority

5.3.5.6 The Authority shall have regulatory oversight of all PASS.

5.3.5.7 The Authority shall issue not later than 60 working days of submission of the protocol, decision letter to the applicant. This may be an approval, conditional approval, deferral or rejection.

5.3.6 Study Protocol

All PASS must be conducted in accordance with the approved protocol; the protocol shall have the following sections:

5.3.6.1 **Title:** informative title including a commonly used term indicating the study design and the medicinal product, substance or drug class concerned, and a sub-title with a version identifier and the date of the last version.

5.3.6.2 **Applicant**: name and address of the marketing authorisation holder or principal investigator.

5.3.6.3 **Responsible parties**: names, titles, qualifications, addresses, and affiliations of all main responsible parties, including the main author(s) of the protocol, the principal investigator, coordinating investigator. A list of all collaborating institutions and investigators should be made available to the Authority.

5.3.6.4 **Abstract**: stand-alone summary of the study protocol including the following subsections: Title with subtitles including version and date of the protocol and name and affiliation of main author, Rationale and background, Research question and objectives, Study design, Population, Variables, Data sources, Sample size, Data analysis, Milestones.

5.3.6.5 **Amendments and updates**: any substantial amendment and update to the study protocol after the start of data collection, including a justification for each amendment or update, dates of each change and a reference to the section of the protocol where the change has been made.

5.3.6.6 **Milestones**: Table with planned dates for the following milestones: Start of data collection, End of data collection, Study progress report(s), Interim report(s) of study results, where applicable, in line with phases of data analyses, Final report of study results and any other important timelines in the conduct of the study should be presented.

5.3.6.7 **Rationale and background**: short description of the safety hazard(s), the safety profile or the risk management measures that led to the initiation or imposition of the study, and short critical review of available published and unpublished data to explain gaps in knowledge that the study is intended to fill. The review may encompass relevant animal and human experiments, clinical studies, vital statistics and previous epidemiologic studies. The review should cite the findings of similar studies, and the expected contribution of the current study.

5.3.6.8 **Research question and objectives**: research question that explains how the study will address the issue which led to the study being initiated or imposed, and research objectives, including any pre-specified hypotheses and main summary measures.

5.3.6.9 **Research methods**: description of the research methods, including.

5.3.6.10 **Study design**: overall research design and rationale for this choice.

5.3.6.11 **Setting**: study population defined in terms of persons, place, time period, and selection criteria, including the rationale for any inclusion and exclusion criteria and their impact on the number of subjects available for analysis. Where any sampling from a source population is undertaken, description of the source population and details of sampling methods should be provided. Where the study design is a systematic review or a meta-analysis, the criteria for the selection and eligibility of studies should be explained.

5.3.6.12 **Variables**: outcomes, exposures and other variables including measured risk factors should be addressed separately, including operational definitions; potential confounding variables and effect modifiers should be specified.

5.3.6.13 **Data sources**: strategies and data sources for determining exposures, outcomes and all other variables relevant to the study objectives, such as potential confounding variables and effect modifiers. Where the study will use an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data should be reported. If data collection methods or instruments are tested in a pilot study, plans for the pilot study should be presented. If a pilot study has already been performed, a summary of the results should be reported. Involvement of any expert committees to validate diagnoses should be stated. In case of a systematic review or meta-analysis, the search strategy and processes and any methods for confirming data from investigators should be described.

5.3.6.14 **Study size**: any projected study size, precision sought for study estimates and any calculation of the sample size that can minimally detect a pre-specified risk with a pre-specified statistical precision.

5.3.6.15 **Data management**: data management and statistical programmes to be used in the study, including procedures for data collection, retrieval and preparation.

5.3.6.16 **Data analysis**: the major steps that lead from raw data to a final result, including methods used to correct inconsistencies or errors, impute values, modify raw data, categorise, analyse and present results, and procedures to control sources of bias and their influence on results; statistical procedures to be applied to the data to obtain point estimates and confidence intervals of measures of occurrence or association, and sensitivity analyses.

5.3.6.17 **Quality control**: description of any mechanisms and procedures to ensure data quality and integrity, including accuracy and legibility

of collected data and original documents, extent of source data verification and validation of endpoints, storage of records and archiving of statistical programmes. As appropriate, certification and/or qualifications of any supporting laboratory or research groups should be included.

5.3.6.18 **Limitations of the research methods**: any potential limitations of the study design, data sources, and analytic methods, including issues relating to confounding, bias, generalizability, and random error. The likely success of efforts taken to reduce errors should be discussed.

5.3.6.19 **Protection of human subjects**: safeguards to comply with national requirements for ensuring the well-being and rights of participants in PASS.

5.3.6.20 **Management and reporting of adverse events/adverse reactions**: procedures for the collection, management and reporting of individual cases of adverse reactions and of any new information that might influence the evaluation of the benefit-risk balance of the product while the study is being conducted.

5.3.6.21 **Plans for disseminating and communicating study results:** including any plans for submission of progress reports and final reports.

5.3.6.22 **References:** An annex should list all separate documents and list or include any additional or complementary information on specific aspects not previously addressed (e.g. questionnaires, case report forms), with clear document references.

5.3.7 Amendments

5.3.7.1 Any amendment to the PASS protocol and study arrangements shall be submitted to the Ethics Committee(s) that originally approved the protocol and the Authority for approval before such amendments are carried out.

5.3.7.2 If such amendments are necessary to protect the life of subjects, an urgent amendment may be carried out, but the investigator shall inform the Ethics Committee(s) and the Authority of such amendments with an immediate phone call, followed by a written report within forty-eight (48) hours.

5.3.7.3 Reports of all amendments shall include but not be limited to the following:

i. Reasons for the amendments.
ii. Possible consequences for subjects already included in the PASS.

iii. Possible consequences for the evaluation of the report.

5.3.7.4 All amendments shall attract a fee which shall be determined as per the MCAZ Fee Schedule.

5.3.8 Reporting Pharmacovigilance Data to the Authority

5.3.8.1 Data relevant to the risk-benefit balance of the product

i The Applicant shall monitor the data generated while the study is being conducted and consider its implications for the benefit-risk balance of the medicinal product concerned.

ii Any new information that may affect the benefit-risk balance of the medicinal product should be communicated to the Authority by an official letter within 7days to the Director-General.

iii Information affecting the risk-benefit balance of the medicinal product may include that arising from an analysis of adverse reactions and aggregated data. This communication should not affect information on the results of studies which should be provided by means of periodic safety update reports (PSURs) or periodic benefit risk evaluation report (PBRER) and in risk management plan (RMP) updates, where applicable.

5.3.8.2 Reporting of adverse reactions/adverse events

i Adverse reactions/adverse events should be reported to the Authority. Procedures for the collection, management and reporting of suspected adverse reactions/adverse events should be put in place and summarized in the study protocol.

ii Adverse Drug Reaction (ADR) reports should be submitted electronically on https://e-pv.mcaz.co.zw. Alternatively, reporting forms may be obtained from the MCAZ offices at 106 Baines Avenues, Harare, Zimbabwe or may be downloaded from the MCAZ website: www.mcaz.co.zw.

iii For fatal or life-threatening, unexpected events during clinical development, the principal investigator (PI) is required to alert the MCAZ as soon as possible but no later than 7 calendar days after first knowledge by the investigator that a case qualifies, followed by a complete report as soon as possible within 8 additional calendar days. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products. Serious, unexpected reactions that are not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days after first knowledge by the principal

investigator that the case meets the minimum criteria for expedited reporting.

5.3.8.3 Study reports:-Annual progress reports, preliminary, final reports and publications of outcomes

i. The Principal investigator is required to submit to the MCAZ, annual progress report, preliminary, final and publication of the study outcome to the MCAZ.
ii. In line with MASCA Chapter 15:03 requirements, "Not later than 30 days after the completion of a study, the person who conducted the trial shall compile and submit to the Secretary through the Authority (MCAZ) a preliminary report on the ethical evaluation of the trial'. In addition to the report referred to above, the person who conducted the trial shall, not later than 90 days after the completion of the trial, compile and submit to the Secretary through the Authority (MCAZ) a comprehensive report or any serious or adverse effects or reaction established by the trial.
iii. The Principal Investigator and/or applicant of the trial/study shall submit monitoring reports, annual renewal applications to the MCAZ at the start of each calendar year. If a study is discontinued, the applicant should inform the Authority with reasons for the termination within 7 working days and a final report should be submitted no later than 90 days.
iv. Where the result of the PASS affects the risk management system or the marketing authorization status of the medicinal product, this shall be communicated to the Authority and steps to incorporate these changes in the RMP and variation to the marketing authorization described.
v. The Authority may also request variation to the risk management system or the marketing authorization after review of the PASS study report.

5.4 Post-authorization efficacy study (PAES)

Post-authorization efficacy studies take place after marketing authorization is granted and the medicine is in general use. They are Phase IV studies, intended to complement efficacy data that is available at the time of the initial authorization, and gather long-term data about how well the medicine works when used widely.

A post-authorisation efficacy study (PAES) may be voluntary or imposed by the Authority. The Authority requests such studies when there are important questions about the efficacy of the medicine that can only be answered once the product is in general use, or when questions arise in the post-authorisation period.

5.4.1 Conditions for conducting PAES

PAES may be initiated by the applicant or requested by the Authority. Conditions under which PAES are conducted are listed below:

5.4.1.1 An initial efficacy assessment based on surrogate endpoints requires verification.
5.4.1.2 In the case of medicinal products used in combination with other medicinal products, there may be a need for further efficacy data to clarify uncertainties.
5.4.1.3 Uncertainties with respect to the efficacy of a medicinal product in certain subpopulations that could not be resolved prior to marketing authorisation.
5.4.1.4 A change in the understanding of the standard of care for a disease or the pharmacology of a medicinal product.
5.4.1.5 The potential lack of efficacy in the long term that raises concerns with respect to the maintenance of a positive benefit-risk balance of the medicinal product.
5.4.1.6 New concrete and objective scientific factors that may constitute a basis for finding that previous efficacy evaluations may need to be significantly revised.

All Post Authorization Studies should be approved by the Ethics Committees and the Authority.

For more information about PAES please refer to sections 5.3.3 to 5.3.8 of the PASS as the same information applies

5.5 Reporting of serious and unexpected ADRs by the Pharmaceutical Industry

Pharmaceutical industry should report all serious and unexpected adverse drug reactions occurring in Zimbabwe as soon as possible, but in no case later than 15 calendar days of initial receipt of the information. In case all the information needed is not available within 15 days, the Applicant should submit an initial report containing at least the minimum data elements required (i.e., patient details, suspected product details, reaction details and the reporter details) in order to meet the expedited reporting time frames. A follow-up report containing more detailed information should be submitted later as soon as this becomes available.

Cases of non-serious ADRs, whether expected or not, are also to be reported to the MCAZ as soon as possible, within a period of 28 calendar days of initial receipt of the information.

Marketing Authorization Holders are required to search widely referenced databases (e.g., Medline, Embase) on weekly basis and submit any case originating from Zimbabwe on registered products to the Authority. Marketing Authorization Holders are also required to search local scientific and medical journals not included in widely referenced databases on scheduled basis depending on the periodicity of such journals and submit any publication identified as coming from Zimbabwe on a registered product to the Authority. Publications should be

accompanied by a copy of the article. If the article describes identifiable patients, ADR forms should be completed for each patient and the publication authors considered as the primary source. Reports from lay press should be handled as spontaneous reports; every attempt should be made to collect minimum information that constitutes a valid ICSR. The same timelines apply as for spontaneous reports. Internet or Digital media under the management of MAH should be screened regularly for adverse reaction reports and report to the Authority within the specified timelines. Reports from non-company sponsored internet sites or social media (e.g. Facebook, WhatsApp, etc) should be assessed to determine whether minimum reporting criteria are met, these should also be treated as spontaneous reports. All safety information that becomes available to the MAH as a result of follow-up activities should also be reported.

ADR reports should be sent to the Authority using the MCAZ e-PV reporting platform that is E2B compatible. An alternative electronic E2B format that is compatible with the WHO VigiBase database may be used. The file format should be .xml, MAHs may send reports in E2B files via e-mail to mcaz@mcaz.co.zw or pvct@mcaz.co.zw.

Foreign individual case safety reports should not be submitted to the Authority on a routine basis but should be reported in the context of a specific safety issue or on specific request by the Authority.

5.6 Safety variations

5.6.1 Summary of Product Characteristics (SmPC) or Package insert (PI) and Patient information Leaflet

Changes to safety aspects of approved labelling information including Summary of Product Characteristics (SmPC) or Package insert (PI) and PIL must be submitted to the MCAZ for approval before implementation. Editorial changes to the PI or SmPC should also be submitted to the MCAZ for approval.

The following documentation is required for SMPC PI/PIL changes/variations:

5.6.1.1 Cover letter addressed to the Director-General summarising the changes and the reasons or Justifications for the changes

5.6.1.2 Tracked version of the PI/PIL indicating the section where the change(s) have been effected

5.6.1.3 Clean version of proposed PI/PIL

5.6.1.4 Proof of approval by a Stringent or reference Regulatory Authority (e.g EMA) if available.

5.6.2 Change(s) to therapeutic indication(s)

A therapeutic indication for a given medicine is the primary source of information for its use. It should clearly state the disease/condition that a medicine is intended to treat and the patient group clearly benefiting from it. MCAZ evaluates the therapeutic indications that applicants apply for as part of their application for a new marketing authorisation or a change to the indication of an existing marketing authorisation.

Addition of a new therapeutic indication or modification of an approved one

In this context a new indication would normally include the following:

5.6.2.1 a new target disease,
5.6.2.2 different stages or severity of a disease,
5.6.2.3 an extended target population for the same disease, e.g. based on a different age range or other intrinsic (e.g. renal impairment) or extrinsic (e.g. concomitant product) factors,
5.6.2.4 change from the first line treatment to second line treatment (or second line to first line treatment), or from combination therapy to monotherapy, or from one combination therapy (e.g. in the area of cancer) to another combination,
5.6.2.5 Change from treatment to prevention or diagnosis of a disease.
5.6.2.6 change from treatment to prevention of progression of a disease or to prevention of relapses of a disease,
5.6.2.7 change from short-term treatment to long-term maintenance therapy in chronic disease.

The following cases CANNOT be applied for as addition of a new indication:

5.6.2.8 The indication of a non-orphan medicinal product is extended to include an orphan indication.
5.6.2.9 Where the strength, pharmaceutical form or route of administration of the medicinal product is changed in parallel to the new indication.

These scenarios require a new market authorisation application.

5.6.3 Documentation to be submitted

The request for the change to therapeutic indication(s) should be submitted with the under listed documentation:

5.6.3.1 Cover letter addressed to the Director-General indicating the changes or the additional indication.
5.6.3.2 Justification of new therapeutic indication.
5.6.3.3 Supporting pre-clinical studies if necessary.
5.6.3.4 Supporting clinical studies.

5.6.3.5 Tracked version of the SMPC PI/PIL indicating the section where the change(s) have been effected.
5.6.3.6 Clean version of proposed SMPC PI/PIL.
5.6.3.7 Proof of approval by a Stringent Regulatory Authority (eg EMA) if available.

Feedback on review of the safety variations will be communicated to the applicant within 60 working days from date of receipt.

5.7 Safety communication

Throughout the life cycle of the medicinal product information relating to the benefit-risk profile of the product may need to be communicated to stakeholders including, regulatory authorities and marketing authorization holders, patients and healthcare professionals who use (i.e. prescribe, handle, dispense, administer or take) medicinal products.

5.7.1 Objectives of Safety Communication

Safety communication aims at:

5.7.1.1 providing timely evidence-based information on the safe and effective use of medicines;
5.7.1.2 facilitating changes to healthcare practices (including self-medication practices) where necessary;
5.7.1.3 improving attitudes, decisions and behaviour in relation to the use of medicines;
5.7.1.4 supporting risk minimization behaviour;
5.7.1.5 Facilitating informed decisions on the rational use of medicines.
5.7.1.6 Further, safety communication should support public confidence in the regulatory system.

5.7.2 Principles of safety communication

5.7.2.1 Should deliver relevant, clear, accurate and consistent messages and reach the right audiences at the right time for them to take appropriate action.
5.7.2.2 Should be tailored to the appropriate audiences (e.g. patients and healthcare professionals) by using appropriate language
5.7.2.3 The need for communicating safety information should be considered throughout the pharmacovigilance and risk management process and should be part of the risk assessment and risk minimisation measures.
5.7.2.4 There should be adequate coordination and cooperation between the different parties involved in issuing safety communications (e.g. competent authorities, other public bodies and marketing authorisation holders).
5.7.2.5 Information on risks should be presented in the context of the benefits of the medicine and include available and relevant information on the seriousness, severity, frequency, risk factors,

time to onset, reversibility of potential adverse reactions and expected time to recovery.

5.7.2.6 Safety communication should address the uncertainties related to a safety concern. This is of relevance for new information which is often communicated while competent authorities are conducting their evaluations; the usefulness of communication at this stage needs to be balanced against the potential for confusion if uncertainties are not properly represented. Information on competing risks such as the risk of non-treatment should be included where appropriate.

5.7.2.7 The most appropriate quantitative measures should be used when describing and comparing risks, e.g. the use of absolute risks and not just relative risks; when comparing risks, denominators should be the same in size. The use of other tools such as graphical presentation of the risk and/or the risk-benefit balance may also be considered.

5.7.2.8 Patients and healthcare professionals should, where possible, be consulted and messages pre-tested early in the preparation of safety communication, particularly on complex safety concerns.

5.7.2.9 Where relevant safety communication should be complemented at a later stage with follow-up communication e.g. on the resolution of a safety concern or updated recommendations.

5.7.2.10 The effectiveness of safety communication should be evaluated where appropriate and possible Safety communications should comply with relevant requirements relating to individual data protection and confidentiality.

5.7.3 Target Audience

5.7.3.1 The primary target audiences for safety communication issued by competent authorities and marketing authorisation holders should be patients, carers and healthcare professionals who use (i.e. prescribe, handle, dispense, administer or take) medicinal products.

5.7.4 Requirements

5.7.4.1 All Safety Communication issued by the applicant or manufacturer shall receive prior approval from the Authority. Application for approval shall include a copy of the proposed communication, the medium of distribution and the targeted audience(s).

5.7.4.2 Safety communication should be effective, that is the message must be transmitted, received and understood by the target audience in the way it was intended, and appropriate action is taken by the target audience.

5.7.4.3 Systems should be put in place to measure the effectiveness of safety communication.

5.7.5 Types of Safety Communication

5.7.5.1 **Direct healthcare professional communication** (DHPC) -is a communication intervention by which important safety information is delivered directly to individual healthcare professionals by a marketing authorisation holder or a competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product. The preparation of DHPCs involves cooperation between the marketing authorisation holder and the competent authority. The agreement will cover both the content of the DHPC and the communication plan including the intended recipients, the timetable, and the channels for disseminating the DHPC.

5.7.5.2 **Communication materials** from competent authorities targeted at healthcare professionals-Alert notices, circular letters etc. These are usually published on the website of the competent authority. They contain the competent authority's recommendations and advice for risk minimisation for healthcare professionals and provide relevant background information. Adequate links to further information can be included (e.g. links to the product information of the concerned medicinal product(s) and, whenever possible, prescription and dispensing systems).

5.7.5.3 **Documents in lay language** to patients and the general public e.g. using a questions & answers format helps patients and the general public to understand the scientific evidence and regulatory actions relating to a safety concern.

5.7.5.4 **Press communication** -Press communication includes press releases and press briefings which are primarily intended for journalists. Reach out to a wider audience & build trust in the regulatory system. Press briefings with journalists should be considered by competent authorities for safety concerns or other matters relating to the safety of medicinal products that are of high media interest or when complex or public-health-sensitive messages need to be conveyed cause unnecessary panic. Should be easily accessible and understandable by the public.

5.7.5.5 **Bulletins and newsletters** - May serve as reminders of previous communications.

5.7.5.6 **Social media and other online communications** - Special attention should be paid to ensure that the accuracy of the information released is not compromised

5.7.5.7 **Publications** in scientific journals and journals of professional bodies.

5.7.5.8 **Others** - patient alert cards, educational material etc.

5.7.6 Content of Safety Communication

The information in the safety communication shall not be misleading and shall be presented objectively. Safety communication should contain:

5.7.6.1 The active substance, brand name/invented name of the medicinal product and the main message of the DHCP should be provided at the top of the letter.

5.7.6.2 Important emerging information on any authorized medicinal product which has an impact on the medicine's benefit-risk balance under any conditions of use; Brief description of the safety concern.

5.7.6.3 The reason for initiating safety communication clearly explained to the target audience;

5.7.6.4 Any recommendations to healthcare professionals and patients on how to deal with a safety concern; eg recommendations for risk minimisation (e.g. contraindications, warnings, precautions of use) and, if applicable, switch to alternative treatment, Recall information, if applicable;

5.7.6.5 Background on the safety concern;

5.7.6.6 When applicable, a statement on the agreement between the applicant and the Authority on the safety information provided;

5.7.6.7 Information on any proposed change to the product information (e.g. the summary of product characteristics (SmPC) or package insert (PI);

5.7.6.8 A list of literature references, when relevant or a reference to where more detailed information can be found;

5.7.6.9 A reminder of the need to report suspected adverse reactions eg "Healthcare Providers are urged to monitor and report any adverse events associated with the use of this medicine to the Medicines Control Authority of Zimbabwe. Adverse Drug Reaction (ADR) reporting forms may be obtained from the MCAZ offices at 106 Baines Avenues, Harare, Zimbabwe or may be downloaded from the MCAZ website: www.mcaz.co.zw. Alternatively, reports can be submitted electronically on https://e-pv.mcaz.co.zw".

5.7.6.10 Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address should be provided.

All safety communication submissions will be processed within 60 working days of receipt of the application or less if it's urgent.

5.8 Changing the category for distribution of a medicine for human use

5.8.1 This section describes the required information that should be submitted to Authority when applying for a change in the category for distribution of a medicine for human use. Currently, Section 39 (Sixth schedule) of Medicines and Allied Substances Control Regulations (SI 150 of 1991) prescribes the categorization of medicines for human use into:

5.8.1.1 Specially Restricted preparations or ("S. R.")- are medicines controlled in terms of Part A of Part VII.

5.8.1.2 Prescription Preparations or ("P. P.") are medicines controlled in terms of Part B of Part VII. These are listed in the ninth schedule Part 1 of MASC-R (section 2 and 74) of 1991.

5.8.1.3 Prescription Preparations ("P.P 10") which are listed in the tenth schedule of MASC-R.

5.8.1.4 Pharmacist Initiated Medicines or ("P. I. M.") are medicines controlled as such in terms of Part C of Part VII. These non-prescription medicines may only be supplied on the recommendation of a pharmacist and proper records need to be maintained. They are listed in the eleventh schedule of MASC-R.

5.8.1.5 Pharmacy Medicines or ('P.") are medicines controlled as such in terms of Part C of Part VII. These are listed in schedule 12 of MASC-R.

5.8.1.6 Household Remedies or ("H. R. ") are medicines suitable for self-medication and which are controlled in terms of Part D of Part VII.

5.8.2 Procedures for changing the category for distribution

Types of Application

5.8.2.1 The re-categorization process depends on the type of application.

i. A major change — requires referral for expert advice, for example the first in a new therapeutic category.
ii. Simple — "me-too" application based on an analogous product, which has already completed the re-categorization procedure.

5.8.2.2 For these purposes, an analogous medicinal product is a medicinal product, which has a Zimbabwe marketing authorization which—

i. has the same active ingredient, route of administration and use;
ii. has the same strength or a higher strength;?
iii. has the same dosage or daily dosage, or a higher dosage or daily dosage; and
iv. is for sale or supply at the same quantity or a greater quantity, as the medicinal product in relation to which the application is made.

Consultation and advice

5.8.2.3 When an application for recategorization is received by the Authority, it is evaluated and presented to the Pharmacovigilance and Clinical Trials Committee (of MCAZ) for decisions and recommendations. For a major recategorization expert advice may be sought from suitably qualified professionals before the application is presented to the Committee.

5.8.2.4 Once the Committee has recommended that recategorization should take place communication is sent to all applicants with the same product for any objections, if there are no objections the product will then be recategorized. The public and healthcare professionals will

be notified of the recategorizations through bulletins, annual reports, and circulars.

5.8.2.5 In the case of applications not approved, the reasons for the decision will be notified to the applicant. Applicants will be given the opportunity to appeal within 30 days by written representation to the Director-General (of MCAZ). The timeline for processing of recategorization applications is 60 working days.

5.8.2.6 The authority may also initiate recategorization in line with the safety changes of the products and in line with recategorizations done with other reference regulators.

5.8.3 **Recategorization from Prescription medicine (PP/PP10) to non-prescription medicine (PIM/P/HR), Recategorization from non-prescription pharmacy medicine (PIM/P) to Household remedy (HR)**

The Medicines and Allied Substances Control Act [Chapter 15:03] and its regulations specifies the criteria by which medicines are categorized into those subjects to medical prescription and those not subject to prescription control. In summary, prescription control is required for medicines where -

5.8.3.1 a direct or indirect danger exists to human health, even when used correctly, if used without medical supervision; or.

5.8.3.2 there is frequently incorrect use which could lead to direct or indirect danger to human health; or.

5.8.3.3 further investigation of activity and/or side-effects is required: or

5.8.3.4 they are normally prescribed by a doctor to be administered parenterally.

5.8.3.5 **Content of recategorization application-**The content of the recategorization application should consist of the following elements which, are addressed in more detail in the sections, which follow:

i. **Recategorization Application Form** (see Appendix 1)
ii. **Recategorization Summary** - a comprehensive summary
iii. **Safety/Efficacy Summary** - supporting safety and where necessary efficacy data.
iv. **Patient Information** - full details of leaflets and
v. **Training and Education** – a summary of what provision has been made for appropriate education and training.
vi. **A critical evaluation** of the proposed pharmacy product demonstrating that none of the prescription criteria apply.
vii. **Pharmacovigilance Plan** – a comprehensive and detailed pharmacovigilance plan.

All cited references must be provided in full with translations where applicable.

5.8.4 Recategorization Summary

The data requirements for the recategorization summary are set out below. This summary should rarely extend beyond two sides of A4 paper but should provide sufficient non-confidential information to allow an informed decision to be made in relation to safe usage of the product as a non-prescription medicine. It will be used for the consultation procedure to provide interested parties with a comprehensive overview of both the essential aspects of the recategorization request and the public health impact of the change.

5.8.4.1 ***Applicant details:*** The company name and address should be provided.

5.8.4.2 ***Product Details:*** Details should be provided of the proposed non-prescription product including name, composition, indications, dosage, age-limits and pack size. The name and MCAZ File/Registration number of the existing prescription product should also be included.

5.8.4.3 ***Rationale for the Recategorization:*** In addition to a concise explanation of the rationale for the switch, the place of the product in the management of the disease in question, in line with current clinical guidelines, should be briefly outlined. Particular attention should be paid to the revised role of the pharmacist and any essential equipment/facilities required to perform this role.

5.8.4.4 ***Support for Recategorization*****:** A brief indication may be submitted of experts or organizations providing written endorsement of the proposal, which can be made available by the applicant on request.

5.8.4.5 ***Specific OTC Requirements****:* Details should be provided of measures incorporated to ensure correct self-diagnosis/self-treatment together with any essential safeguards required in order to prevent incorrect usage. This information will include changes such as additional advice or warning statements, any restrictions on indications, contraindications, dose, pack, length of treatment etc and clear statements about circumstances requiring physician intervention and the action needed if symptoms do not respond or if an adverse reaction occurs.

5.8.4.6 ***Safety Profile*****:** An outline is required of the safety profile including product utilisation / patient exposure details. The major risk factors associated with the product should be summarized and risk-benefit briefly analysed paying particular attention to 'at risk' groups and to know drug interactions. Hazards arising from therapeutic misuse, whether accidental or deliberate, should be indicated including those arising from misdiagnosis, overdose or delay in receiving medical attention.

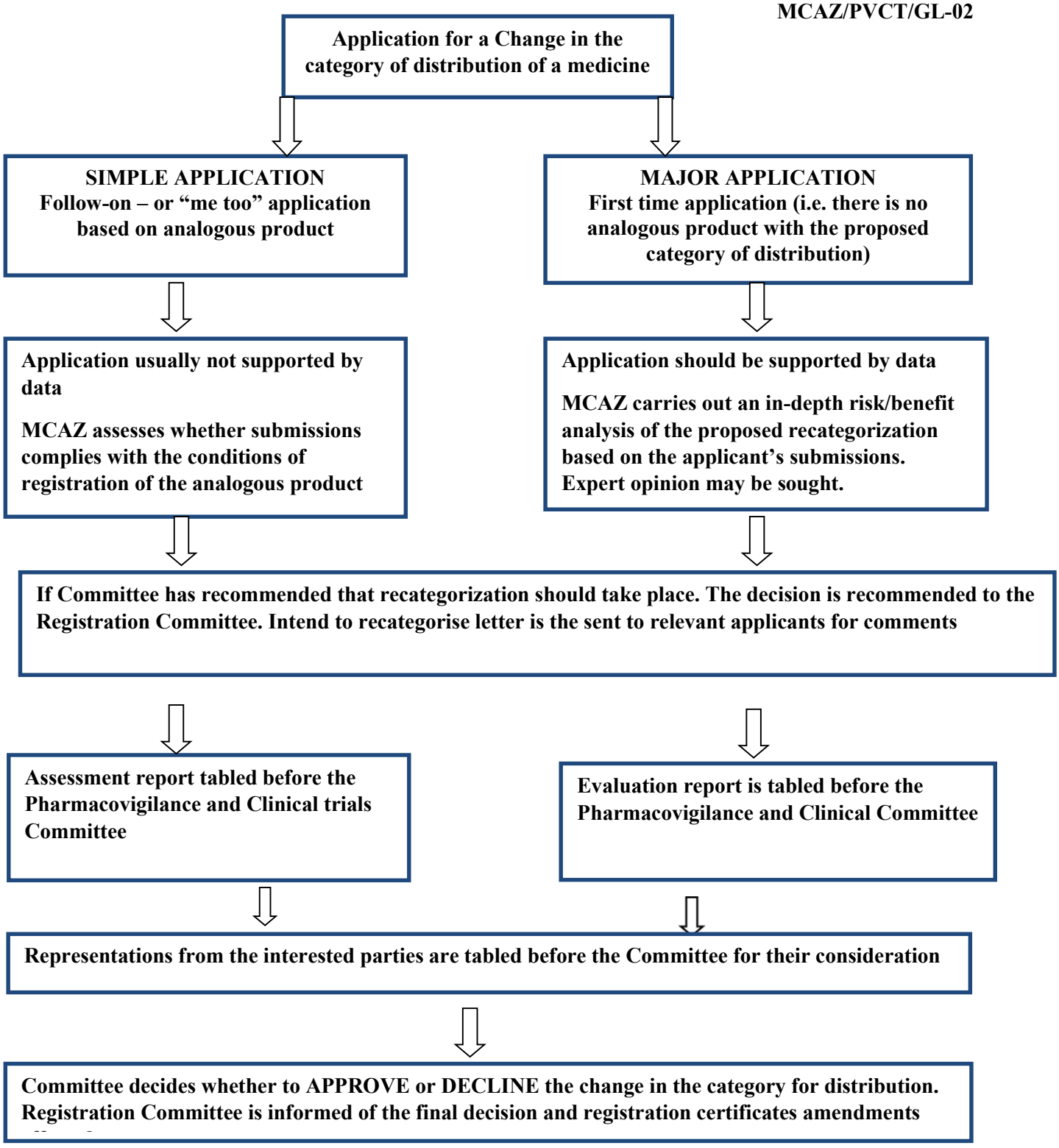

FIGURE 1: STEPS INVOLVED IN PROCESSING AN APPLICATION FOR CHANGE IN CATEGORY OF DISTRIBUTION OF A MEDICINE

5.8.5 Safety/Efficacy Summary

5.8.5.1 The extent of the supporting safety data required will depend on experience with the product and the availability to the applicant of recent Periodic Safety Update Reports (PSURs). Where available, summaries from PSURs should be submitted to MCAZ.

5.8.5.2 Experience in terms of patient exposure to the product needs to be considerable allowing the safety profile to be fully established. Full details of availability, classification for sale and patient exposure should be provided for all countries where marketed.

5.8.5.3 A safety profile should be drawn up based on the following data: -

i. Spontaneous reports of adverse reactions
ii. Post-marketing surveillance studies
iii. Clinical trials
iv. Published literature
v. Safety reviews.

5.8.5.4 Data obtained in Zimbabwe should be distinguished from that obtained from other countries and, for non-Zimbabwe data, details must be provided in relation to differences in product or usage characteristics.

5.8.5.5 Adverse drug reactions to the proposed non-prescription product should normally be minor and should cease on discontinuing therapy. The problems of extrapolating data from a 'prescription only' population to a 'non-prescription' population should be addressed. Comparison of safety with other medicines available in the Zimbabwe without prescription may be helpful.

5.8.5.6 Where pharmaceutical forms or doses to be used have received only limited use, it may be possible to extrapolate from data relating to other presentations and full justification for this approach must be given when used.

5.8.5.7 Reports of therapeutic overdose, misuse or abuse whether deliberate or accidental, should be reviewed. In the case of misuse, the consequence of delay in seeking medical attention should be addressed.

5.8.5.8 Drug interactions may have additional consequence for non-prescription products and these should be reviewed in the light of the recategorization proposal. Attention should be paid to any OTC products the patient may already be using including herbal remedies and nutritional supplements.

5.8.5.9 Efficacy data is only required when indications, dosages or age ranges differ from the authorized product. Pharmacokinetic or pharmacodynamics data are required if a different pharmaceutical form is used.

5.8.5.10 A suitable time period for treatment should be given, with justification, and should be reflected in the pack size proposed for the non-prescription product.

5.8.6 Patient Information

5.8.6.1 Drafts of Patient Information Leaflets (PILs) and packs should be submitted. Those used for the Prescription product will normally require amendment to ensure safe use as a non-prescription product. Clear instructions to aid correct diagnosis and prevent misdiagnosis will be needed.

5.8.6.2 Additional precautions and warnings may be necessary due to the absence of medical supervision, e.g. the action to be taken if no response is obtained and the circumstances requiring pharmacist and/or medical advice.

5.8.6.3 In all cases labelling and patient information leaflets must be supplied which are compliant with requirements of section SI 150 of MASC-R.

5.8.6.4 The proposed product label and patient information are important elements of the application and will be reviewed by the MCAZ to confirm that clear and comprehensive information has been provided which will effectively protect patients from any safety hazards.

5.8.6.5 The patient information leaflet should take full account of the circumstances of use and should provide warnings, as appropriate for use without medical supervision, e.g. limiting duration of treatment, when to seek medical advice etc.

5.8.6.6 The written information should effectively minimize the risk of use where a product is contraindicated or where problems could occur. The applicant should ensure that adequate instructions are included and that all contraindications, precautions and warnings are clearly described in lay terms and prominently printed in the leaflet. In order to minimize risk and maximize benefit, situations where the product must not be used should be given equal prominence on the label and in the leaflet to those in which it may be used.

5.8.6.7 The patient is likely to need guidance on action to take if the medicine does not have the desired effect or causes adverse effects. The Patient Information Leaflet should ensure that appropriate action by the patient is recommended to provide for the absence of medical supervision.

5.8.6.8 Promotional material should comply with the requirements of the Medicines and Allied Control Act [MASCA - Chapter 15:03] and its regulations. It is helpful for advertising plans to be briefly outlined. MASCA requires pre-submission of all medicine-related advertisements to MCAZ, for approval before issue, of all such material.

5.8.7 Training and Education

5.8.7.1 Applicants should review the information and training needs of health care professionals to enable them to support and monitor the patients and clearly identify how such needs will be met.

5.8.8 Clinical Expert Report

The Expert is expected to make an objective and impartial assessment of the application in the light of current scientific knowledge and to confirm that the safety data provided is adequate to support recategorization. At least two systematic review articles and meta-analysis from peer-reviewed journals are acceptable in the place of a clinical expert report. Regardless of the approach that is used, in both cases the Expert should critically evaluate the proposed non-prescription product in the light of the criteria for prescription control and demonstrate why none of the criteria apply. In considering the criteria the factors outlined below should be addressed.

A **First Prescription Medicines Criterion:** Likely to present a danger either directly or indirectly, even when used correctly, if utilized without medical supervision.

5.8.8.1 ***Direct danger:*** A direct danger may be present if the product causes adverse reactions that are important because of their seriousness, severity or frequency or because the reaction is one for which there is no suitable preventative action such as the exclusion of a clearly identifiable risk group. In addition to the product's safety profile, it may be helpful to consider the benefit-to-risk in relation to that for similar products already available as non-prescription medicines for the same indication. One member of a class that causes adverse reactions more frequently than other members of the class may be unsuitable for recategorization for the same indication. Consideration should also be given to the danger arising from drug interactions with commonly used medicines and how these may be prevented.

5.8.8.2 ***Indirect danger****:* An important example of an indirect danger is when symptomatic treatment might mask an underlying condition requiring medical attention, for example cancer or heart disease. Consideration should be given to whether an indirect danger might exist and if so, whether the risk, its frequency and the seriousness of the consequences would make recategorization unacceptable. Additional warnings such as a recommendation to seek medical advice if symptoms persist beyond a stated time period may be necessary in such instances.

Another important example of an indirect danger would be the increased risk of development of bacterial resistance in the community as a result of wider use of antibiotics without medical supervision. Treatments may also present an indirect danger when

particular symptoms are outward manifestations of a diverse range of underlying pathologies. If the patient cannot easily self-diagnose the cause of such symptoms, it may be inappropriate to provide symptomatic treatment without management of the underlying disease. Special attention should be paid to the possibility of serious asymptomatic damage in chronic conditions.

5.8.8.3 ***Self-diagnosis*****:** For Recategorization to OTC It is important that the conditions or symptoms for which the product is indicated can be correctly diagnosed without medical supervision or can be easily recognized following initial medical diagnosis. The problem of excluding conditions with similar symptoms but unsuitable for treatment with the product in question may need to be addressed. Appropriate patient information and/or pharmacist advice may be able to influence the ability to correctly self-diagnose. Patients should be able to understand the natural course of the disease and the possibility and consequences of reoccurrence. They should also be able to recognize contraindications and understand essential precautions and warnings. Experience in such issues in relation to other medicines may provide important supplementary information.

5.8.8.4 ***Risk of misuse:*** A high incidence of conditions listed as contraindications, extensive precautions and warnings or a high rate of usage of interacting drugs in the population of patients likely to use the drug may increase the incidence and risk of misuse. It is important that the danger to health is small if the patient uses the product when it is not indicated, exceeds the recommended dose or recommended length of treatment or fails to heed the contraindications or warnings. Consideration of the consequences of misuse is an important component of the overall safety profile of the product. Concerns over the risk of misuse are lessened where the product causes only few, non-serious side effects. In this situation, while the risk-to-benefit may be unfavorable to the patient who uses the product incorrectly, the overall risk-to-benefit for availability of the medicine in the community without prescription may be favorable. It may also be necessary to consider whether incorrect use might lead to an indirect risk, e.g. a delay in seeking medical treatment, and if so, whether the consequences to the patient would be important.

B **Second Prescription Medicines Criterion:** Frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health

5.8.8.5 When a product or substance is known to be used frequently incorrectly, non-prescription pharmacy only status is not appropriate. Recognized widespread misuse of a product or substance classified as a pharmacy medicine could lead to its recategorization as a prescription medicine.

C **Third Prescription Medicines Criterion:** Contain substances or preparations thereof the activity and/or side-effects of which require further investigation

5.8.8.6 ***Limited experience*****:** Further investigation is likely to be necessary where the number of patients exposed is relatively small, for example when a medicine has only recently been authorized, because there is limited experience of the product under normal conditions of use. Even if clinical trial data are extensive and reassuring, it is important to have evidence of safety where the product is being used without the exclusion of certain groups of patients imposed by the design of clinical trials (e.g. the elderly, children and those with certain medical conditions.).

5.8.8.7 ***New strength, dose, route of administration, age group or indication***: Further investigation is also necessary where it is proposed that the substance will be available without prescription as follows: -

i. in a new strength,
ii. at a new dose,
iii. using a new route of administration,
iv. exposing a different patient age group, or
v. for a new indication, particularly when the indication has not been previously authorized for a non-prescription product.

Even though the safety profile of the medicinal product as it is presently marketed, is relevant, re-evaluation of risk-to-benefit according to the proposed use is necessary. This may be difficult because the product will not have been widely available for the new indication or new dosage. It may nevertheless be possible to extrapolate from the known safety of the existing prescription product, particularly if there are few side-effects and/or where doses proposed for non-prescription supply are lower and the population is a sub-group of the patient group treated on prescription.

D **Fourth Prescription Medicines Criterion:** Are normally prescribed by a doctor or dentist to be administered parenterally.

5.8.8.8 Parenteral administration involves breaching the skin or mucosa. Products for parenteral administration are not appropriate for availability without medical supervision because of the additional risks and complexity of this route of administration.

5.8.9 Pharmacovigilance plan

5.8.9.1 Where there is potential or identified risks relating to the reclassification of the method of sale and supply of a medicine and it is proposed that such risks can be managed with the intervention of a pharmacist, risk minimisation measures may be required in support of the application for reclassification.

5.8.9.2 Risk minimisation strategies should be outlined where appropriate. In some situations, where an expanded role for the pharmacist is considered, details of any literature/educational materials that the pharmacist might use or provide to the patient should be appropriately justified and included in the application. The SmPC, label and package leaflet are the primary reference documents for information and should form the basis for any educational materials.

5.8.10 Additional considerations

5.8.10.1 The Expert may need to take account of the other factors that influence legal status as outlined in Medicines and Allied Substances Control Act (Chapter 15:03) and its regulations. This includes whether the substance is a narcotic or a psychotropic substance or might be abused leading to addiction or misused for illegal purposes.

5.8.10.2 In general, for some medicines, supply without a medical prescription may be acceptable if additional restrictions are introduced, e.g. limiting the maximum single dose, the maximum daily dose, the strength, the pharmaceutical form, the circumstances of use, the type of packaging and/or pack size.

5.8.10.3 If restrictions to the maximum dose or maximum daily dose are introduced in order to protect against a danger when the medicine is used either correctly or incorrectly, it is necessary to confirm that the restricted dose retains the efficacy and the favourable benefit-to-risk of the full dose.

5.8.10.4 Consideration should also be given to the need for restrictions on the strength, pharmaceutical form, circumstances of use, pack size, or a combination of these to provide a safeguard against incorrect use including overuse or overdose or against a delay in seeking medical attention. When pack size is restricted, the proposed pack must be compatible with the intended duration of use.

5.9 Monitoring of implementation of Pharmacovigilance aspects by Pharmaceutical companies

5.9.1 Introduction

5.9.1.1 An appropriate system of safety monitoring shall be put in place by each Marketing Authorization Holder or manufacturer of registered products in order to assume responsibility and liability for products on the market and to ensure that appropriate action can be taken when necessary.

5.9.1.2 A pharmacovigilance system is defined as a system used by an organization to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorized medicinal products and detect any change to their risk-benefit balance. A pharmacovigilance system, like any system, is characterized by its structures, processes and outcomes.

5.9.1.3 In addition to spontaneous ADR reporting, the MAH or manufacturer shall put in place pharmacovigilance measures to actively monitor the safety of their products in clinical practice for a period specified by the Authority. The MAH or manufacturer shall permanently and continuously have at his disposal an appropriately Qualified Person Responsible for Pharmacovigilance (QPPV) or Responsible Personnel for PV.

5.9.2 Critical pharmacovigilance processes

The following pharmacovigilance processes should be considered as critical:

5.9.2.1 continuous safety profile monitoring and benefit-risk evaluation of authorised medicinal products;

5.9.2.2 establishing, assessing and implementing risk management systems and evaluating the effectiveness of risk minimisation where required;

5.9.2.3 collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of individual case safety reports (ICSRs) from any source;signal management;

5.9.4.4 scheduling, preparation (including data evaluation and quality control), submission and assessment of periodic safety update reports;

5.9.2.5 meeting commitments and responding to requests from the Authority, including provision of correct and complete information;

5.9.2.6 interaction between the pharmacovigilance and product quality defect systems;
5.9.2.7 Communication about safety concerns between marketing authorisation holders and the Authority, in particular notifying changes to the risk-benefit balance of medicinal products;
5.9.2.8 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;
5.9.2.9 keeping product information up-to-date with the current scientific knowledge, including the conclusions of the assessment and recommendations from the Board;
5.9.2.10 Implementation of variations to marketing authorisations for safety reasons according to the urgency required.

5.9.3 Responsible person for PV or QPPV

Every MAH or manufacturer who has registered a medicine in Zimbabwe shall designate a responsible person for PV or QPPV to oversee the pharmacovigilance system. The individual shall be responsible for the safety of the medicines marketed by an applicant or manufacturer in Zimbabwe. However, the MAH retains the overall responsibility for their products and is answerable to any issues regarding the products. All feedback/responses will be addressed to the MAH/applicant in line with our legislation. The responsible person for PV or the QPPV may be resident in Zimbabwe or be an external party. For administrative purposes the MAH should notify the MCAZ in writing who their responsible person for PV or the QPPV is, their curriculum vitae, contact details and their responsibilities. The responsible person should be adequately qualified to execute her or his duties (healthcare professional with a degree in Medicine, Pharmacy, Nursing, Biomedical Sciences, or any other healthcare professional degree recognized by the Authority). The QPPV should have received a formal training in pharmacovigilance recognized by the Authority and should have knowledge of the Zimbabwe pharmacovigilance legislation and guidelines and other international standards for Pharmacovigilance.

The MAH should:

i. Provide comprehensive training in Pharmacovigilance to the QPPV
ii. Ensure that the QPPV has sufficient authority to Implement pharmacovigilance activities, provide inputs into Risk Management Plan when necessary, provide inputs into the preparation of regulatory documents to emerging safety concerns (e.g. variations, urgent safety restrictions and as appropriate, communication to Patients and Healthcare Professionals)

iii. Ensure that there are appropriate processes, resources, communication mechanisms and access to all sources of relevant information in place for the fulfilment of the QPPV's responsibilities and tasks.
iv. Notify the Authority of the absence of the QPPV not later than 30 days after the position becomes vacant.
v. Have a written contract with the QPPV.

5.9.3.1 Responsibilities of QPPV

i. The QPPV should have oversight of the pharmacovigilance system in relation to structure and proper functioning and be able to ensure that all responsibilities are performed well and to ensure in particular the following system components and processes, either directly or through supervision.
ii. The QPPV should act as a point of contact for the MAH on all matters relating to pharmacovigilance and safety of marketed products including pharmacovigilance inspections. He or she should be available during PV inspections.
iii. Establishment and maintenance of a system which ensures that information about all suspected adverse drug reactions/ events which are reported to the personnel of the marketing authorization holder and to the medical representatives is collected, collated and assessed for onward submission to the Authority.
iv. The QPPV should have access to the pharmacovigilance system master file (PSMF) and be in a position of authority to ensure and to verify that the information contained in the PSMF is an accurate and up-to-date reflection of the pharmacovigilance system under the QPPV's responsibility.
v. 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)
vi. Prepare the following documents for submission to the Authority:
    a. Adverse Drug Reaction reports/ individual case safety reports (ICSRs)
    b. Periodic Safety Update Reports (PSURs)/Periodic Benefit-Risk Evaluation Report PBRER), when necessary
    c. Company-sponsored pre-and post-registration safety and efficacy study reports
    d. Risk Management Plan (RMP), when necessary
vii. Ensure that any request from the Authority for additional information deemed necessary for the evaluation of the risk–benefit

afforded by a marketed product, is provided to MCAZ promptly and fully.

viii. Ensure safety monitoring oversight of the marketed products and any emerging safety concerns

5.9.3.2 Training of personnel for pharmacovigilance

i. Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes by an organisation is intrinsically linked with the availability of a sufficient number of competent and appropriately qualified and trained personnel.

ii. All personnel involved in the performance of pharmacovigilance activities shall receive initial and continued training. For marketing authorisation holders, this training shall relate to the roles and responsibilities of the personnel. The organisation shall keep annual 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.

iii. The training should support continuous improvement of relevant skills, the application of scientific progress and professional development and ensure that staff members have the appropriate qualifications, understanding of relevant pharmacovigilance requirements as well as experience for the assigned tasks and responsibilities. All staff members of the organisation should receive and be able to seek information about what to do if they become aware of a safety concern.

iv. Adequate training should also be considered by the organisation for those staff members to whom no specific pharmacovigilance tasks and responsibilities have been assigned but whose activities may have an impact on the pharmacovigilance system or the conduct of pharmacovigilance. Such activities include but are not limited to those related to clinical trials, technical product complaints, medical information, terminologies, sales and marketing, regulatory affairs, legal affairs and audits.

5.9.4 Record management

5.9.4.1 The MAH shall record all pharmacovigilance information and ensure that it is handled and stored so as to allow accurate reporting, interpretation and verification of that information.

5.9.4.2 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.

5.9.4.3 The record management system should support:

i. the management of the quality of pharmacovigilance data, including their completeness, accuracy and integrity;
ii. timely access to all records;
iii. effective internal and external communication; and
iv. 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.

5.9.4.4 In addition, marketing authorisation holders shall establish mechanisms enabling the traceability and follow-up of adverse reaction reports. In this context, it should be ensured that the fundamental right to personal data protection is fully and effectively guaranteed in all pharmacovigilance activities in conformity with legal provisions.

5.9.4.5 As part of a record management system, specific measures should therefore be taken at each stage in the storage and processing of pharmacovigilance data to ensure data security and confidentiality.

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

5.9.5 Pharmacovigilance Site Master File (PSMF)

The structure and format of the PSMF should be in-line with the EMA GVP Module II – Pharmacovigilance system master file (Rev 2).

https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-ii-pharmacovigilance-system-master-file-rev-2_en.pdf

5.10 Pharmacovigilance inspections

To ensure that Marketing Authorization Holders (MAH) and manufacturers comply with pharmacovigilance regulatory requirements and to facilitate compliance, the Authority may conduct Pharmacovigilance inspections in conjunction with routine GMP inspections or remotely. A risk-based approach will be considered for PV inspections. Documents inspected will include the Pharmacovigilance Site Master File and other relevant PV documents and systems.

5.10.1 Objectives of Pharmacovigilance Inspections

5.10.1.1 Improve pharmacovigilance system established by MAHs.

5.10.1.2 Ensure compliance with the pharmacovigilance obligations by manufactures and MAH to protect public health and safety.

5.10.1.3 Enforce regulatory requirements.

5.10.2 The inspection Programme

5.10.2.1 The Authority will perform Pharmacovigilance inspections for MAHs and/ manufacturers based on a risk-based approach.

5.10.2.2 Factors which may affect inspection scheduling may include but not limited to the following:

Inspection related:

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

product related:

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

marketing authorisation holder related:

i. marketing authorisation holder that has never been subject to a pharmacovigilance inspection;
ii. marketing authorisation holder with many products on the market in Zimbabwe;
iii. resources available to the marketing authorisation holder for the pharmacovigilance activities they undertake;
iv. marketing authorisation holder with no previous marketing authorisations in Zimbabwe;
v. negative information and/or safety concerns raised by competent authorities, other bodies outside Zimbabwe or other areas (i.e. GCP, GMP, GLP and GDP);
vi. changes in the marketing authorisation holder organisation, such as mergers and acquisitions;

pharmacovigilance system related:

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

i.

5.10.3 Inspection process

5.10.3.1 Pharmacovigilance inspections should be well planned, coordinated, conducted, and reported on, follow-up and documented in accordance with prescribed inspection procedure.

5.10.3.2 A preliminary notification to the manufacturer or the MAH about the scheduled inspection and the list of pertinent documents to facilitate the inspection may be shared by the Authority at least 14 days to the scheduled date of inspection. The date for the inspection will be agreed with the MAH.

5.10.3.3 The Authority may request for the following documents prior to or during the inspection. This may include but not limited to;

i. Curriculum vitae, job descriptions and training records for QPPV and any other PV personnel.
ii. Contract between the manufacturer or the MAH and the QPPV
iii. Organization charts/organograms (with names and job titles);
iv. Procedural documents (e.g. Standard Operating Procedures, Job descriptions, terms of reference etc.);
v. Standard training material and presentations;
vi. Minutes of meetings specific to Pharmacovigilance;
vii. Individual adverse reaction cases files and adverse event reports;

viii. Recent PSURs/PBRERs for marketed products where available;
ix. RMPs for selected products when applicable;
x. Pharmacovigilance System Master File (PSMF) .

5.10.3.4 Deficiencies found during the Pharmacovigilance inspection are graded as follows;

i. **Critica**l: A deficiency in Pharmacovigilance systems, practices or processes that could either adversely affect the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation or regulatory offence of the MCAZ guidelines.
ii. **Major:** A deficiency in Pharmacovigilance systems, practices or processes that could either potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of the MCAZ guidelines.

iii. **Minor**: A deficiency in Pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients. Lots of minor non-compliance may add up to a major non-compliance.

5.10.3.5 In general, preliminary findings will be communicated at the closing meeting. An inspection report is then prepared and reviewed internally to ensure consistency of classification of deficiencies prior to issue of the final report.

5.10.3.6 The report is sent to the MAH, within 14 working days of the inspection. Following the issue of the inspection report, the manufacturer or MAH is requested to respond to any deficiencies identified and to provide the Authority with an appropriate corrective action plan (CAP) within 14 working days.

5.11 Reliance Model

5.11.1 The MCAZ continually ensures the safety of marketed products through its established pharmacovigilance system.

5.11.2 To ensure that safety issues are promptly identified, and the necessary interventions implemented, the MCAZ consider vigilance related decisions, reports or information from other countries, regional or international bodies such as WHO in making decisions on the safety and effectiveness of medical products.

5.11.3 The regulatory decisions by the MCAZ – leveraging safety decision from well –resourced or reference NRAs - are geared towards ensuring appropriate and safe use of registered medical products. The MCAZ considers vigilance reports and decisions from the following:

5.11.3.1 WHO;
5.11.3.2 WHO listed countries;
5.11.3.3 any other countries or bodies considered to be trustworthy and deemed necessary by the Authority.

For more information on reliance model, please refer to the MCAZ reliance policy and guideline.

6.0 KEY RELEVANT DOCUMENTS

6.1 Medicines and Allied Substances Control Act (MASCA) [Chapter 15:03]
6.2 ICH E2C (R2) - Periodic benefit-risk evaluation report (PBRER)
6.3 ICH E2E - Pharmacovigilance Planning
6.4 Guideline on good pharmacovigilance practices (GVP) Module V –Risk Management systems (Rev 2)
6.5 Guideline on good pharmacovigilance practices (GVP)Module VIII – Post-Authorisation safety studies (Rev 1)
6.6 EMA Guidelines for "Changing the Classification for the supply of a medicinal Product for human use" (1998).
6.7 MHRA guidance How to change the legal classification of a medicine in the UK
Guideline on good pharmacovigilance practices (GVP)Module II – Pharmacovigilance system master file (Rev 2)

7.0 HISTORY

<table>
<tr><th colspan="3">DOCUMENT HISTORY</th></tr>
<tr><td>Revision Number</td><td>Date Approved</td><td rowspan="2">Date Reviewed: February 2022

Reason for Change and Amendments
Continuous improvement in line with current WHO GBT indicators

The following changes/amendments were done from Revision 0 to Revision 1

5.1.2.1 Changed from
PSURs/PBRERs are generally NOT requested routinely for generic products. Please note that PSURs/PBRER shall be submitted ONLY when this is given as a condition in the marketing authorisation of the product or at any point post authorisation when requested by the Authority on the basis of safety concerns or when the Authority deems it necessary. This condition will be communicated to the applicant or MAH. Not all products are given this condition. A risk based approach is used to determine whether submission of PBRER or PSUR should be a condition for registration of the product. However for those products which are not given this condition if a regulatory decision is made by other stringent regulatory agencies such as safety variation or DHCP letters the applicant would be required to submit such variations or information to the Authority for approval for implementation in Zimbabwe.
5.1.2.1 Changed to
PSURs/PBRERs are generally NOT requested routinely. Please note that PSURs/PBRER shall be submitted ONLY when this is given as a condition in the marketing authorisation of the product or at any point post authorisation when requested by the Authority on the basis of safety concerns or when the Authority deems it necessary. This condition will be communicated to the applicant or MAH. Not all products are given this condition. A risk based approach is used to determine whether submission of PBRER or PSUR should be a condition for registration of the product.

5.1.2.2 Changed from</td></tr>
<tr><td>0</td><td>March 2021</td></tr>
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		For New Chemical Entities (NCEs) and when given a condition/ requested, PSURs/PBRERs should be submitted as stated below unless otherwise specified by the Authority. i. Every 6 months for the first two years and thereafter 3 yearly ii. Immediately upon request by the Authority. **5.1.2.2 Changed to** When given as a condition of registration or when requested by the Authority, PSURs/PBRERs should be submitted as stated below unless otherwise specified by the Authority. i. Every 6 months for the first two years, yearly for the following 2 years, and at 3-year intervals thereafter. ii. When requested by the Authority, PSURs/PBRERs must be submitted within 30 calendar days of the request. **5.2.4.1 Changed from** Risk management plans are generally NOT requested routinely for generic products. **5.2.4.1 Changed to** Risk management plans are generally NOT requested. **5.2.4.2 Changed from** **Please note** that a risk management plan shall be submitted **ONLY** for new chemical entities or complex products, when this is given as a condition at the marketing authorisation of the product or at any point post authorisation when requested by the Authority on the basis of safety concerns or when the authority deems it necessary. This condition will be communicated to the applicant or MAH. A risk based approach is used to determine whether submission of a risk management plan should be a condition for registration of the product. **5.2.4.2 Changed to** Please note that a risk management plan shall be submitted **ONLY** when this is given as a condition at the marketing authorisation of the product or at any point post authorisation when requested by the Authority on the basis of safety concerns or when the Authority deems it necessary. This condition will be communicated to the applicant or MAH. A risk-based approach is used to determine whether submission of a risk management plan should be a condition for registration of the product.

		RMP submission should occur within 90 days from the date of request, or as specified by the Authority. A risk-based approach is used to determine whether submission of a risk management plan should be a condition for registration of the product. **5.3.8.2 section iii has been added** **5.5 has been added**

APPENDICES

APPENDIX I: APPLICATION FOR RECATEGORISATION

CHANGE IN THE CATEGORY OF DISTRIBUTION: FROM [ ] TO [ ]

Products INN Name:	
Product's Trade Name:	
MCAZ Registration Number:	
Name and Address of the applicant:	
Name and address of the manufacturer:	
Recategorisation fee Submitted:	**[ ] Yes** **[ ] No**
Is this application based on an analagous product?	**[ ] Yes** **[ ] No**
If yes, state product name and the MCAZ Registration number of analagous product: **……..…..(Reg. No……)**	

APPENDIX II: APPLICATION FORM FOR DESIGNATION AS A QPPV

Application Form for designation as a Qualified Person for Pharmacovigilance (QPPV)

A. Particulars of the QPPV:

1. Name …….

2. Postal Address ……

3. Tel ……..…..

4. Educational Qualification / Profession

   ……...

5. Date of Formal Designation as a QPPV

   ……...

6. Date of Expiration of designation as a QPPV

   ……...

B. Employment History as a Qualified Person for Pharmacovigilance

No.	Name of Marketing Authorization Holder	Period (dd/mm/yyyy-dd/mm/yyyy)

C. Continuing Professional Development Undertaken within the last three years

No.	Name of Training Programme	Institution	Period (dd/mm/yyyy-dd/mm/yyyy)	Certificate Awarded (attach copies)

Declaration

I/We, the undersigned, hereby declare that all information contained herein is correct and true.

Name of QPPV: ……

Signature: ……..

Date: …….

If QPPV is designated to a company

Name of Director of MAH ……..

Signature: ……

Date: …….

Official Stamp: