Zambia Medicines Regulatory Authority

GOOD VIGILANCE PRACTICE GUIDELINES

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i. Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AR	Adverse Reaction
ATC	Anatomical Therapeutic Chemical
ATMP	Advanced Therapy Medicinal Product
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CIOMS	Council for International Organisations of Medicinal Sciences
DHPC	Direct Healthcare Professional Communication
GVP	Good Vigilance Practices
IBD	International Birth Date
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Report
ISO	International Organisation for Standardization
LQPPV	Local Qualified Person for Pharmacovigilance
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
PASS	Post Authorisation Safety Studies
PBRER	Periodic Benefit Risk Evaluation Report
PL	Package Leaflet

PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report.
PT	Preferred Term
PV	Pharmacovigilance
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
WHO	World Health Organisation
ZAMRA	Zambia Medicines Regulatory Authority

ii. Definitions

In this guideline, unless the context otherwise states:

Abuse - means a pattern of substance use that is maladaptive or harmful, often continuing despite knowledge of persistent or recurrent social, occupational, psychological, or physical problems caused or worsened by the substance use. This includes using drugs in situations that are physically hazardous, such as driving, or in ways that interfere with personal, family, or social responsibilities;

Act - means the Medicines and Allied Substances Act No 3 of 2013;

Advanced Therapy Medicinal Product - means a medicine or allied substance for human use that is either a gene therapy medicine or allied substance, a somatic cell therapy product or a tissue engineered product;

Adverse event - means: -

(a) any untoward medical occurrence that may be present during use or treatment with a medicine or allied substance whether or not related to the use or treatment, including any unfavorable and unintended sign,

symptom, abnormal laboratory finding or disease temporarily associated with the use of the medicine or allied substance; or

(b) in the case of blood and blood products, any undesirable or unintended occurrence associated with transfusion or donation including incidents, near misses, errors, deviations from standard operating procedures and accidents;

Adverse reaction - means a response to a medicine or allied substance which is noxious and unintended including a response arising from:

(a) the use of a medicine or allied substance within the terms of the marketing authorisation;

(b) the use of a medicine or allied substance outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse and medication errors;

(c) occupational exposure to a medicine or allied substance; and

(d) in the case of blood and blood products, unintended response in a –

(i) donor during collection of blood; or

(ii) patient during transfusion of blood or blood components;

Synonyms: Adverse drug reaction (ADR), Suspected adverse (drug) reaction, Adverse effect, Undesirable effect

Audit - means a Systematic, independent and documented process for obtaining objective evidence and evaluating it objectively to determine the extent to which the audit criteria are fulfilled (see ISO 19011);

Authority - means the Zambia Medicines Regulatory Authority;

Benefit-risk balance - is an evaluation of the positive therapeutic effects of the medicine or allied substance in relation to the risks, i.e. any risk relating to the quality, safety or efficacy of the medicine or allied substance as regards patients' health or public health;

Clinical Trial - means any interventional study or investigation in or involving human participants intended to:

(a) discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational medicine or allied substance; and/or to identify any adverse events or reactions to an investigational medicine or allied substance; and/or to study absorption, distribution, metabolism and excretion of

an investigational medicine or allied substance with the objective of ascertaining its safety and/or efficacy; or

(b) test new procedures that may prevent, detect, or diagnose, treat or manage diseases or conditions to determine if the procedure is safe or effective;

Closed Signal - in periodic benefit-risk evaluation reports, a signal for which an evaluation was completed during the reporting interval;

Company Core Data Sheet - for medicines and allied substances, a document prepared by the MAH containing, in addition to safety information, material related to indications, dosing, pharmacology and other information concerning the product;

Company Core Safety Information - for medicines and allied substances, all relevant safety information contained in the company core data sheet prepared by the MAH and which the MAH needs to be listed in all countries where the company markets the product, except when the Authority specifically requires a modification;

Compassionate Use - making a medicine or allied substance available for compassionate reasons for a group of patients with

a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicine or allied substance (the medicine or allied substance concerned must either be subject of an application for a Marketing Authorisation or must be undergoing clinical trials);

Consumer - means a primary source who is not a healthcare professional. Examples include a patient, patient representative (including a legal representative), caregiver, friend, or relative of a patient (ICH E2D (R1);

Data lock point - for a periodic safety update report (PSUR/PBRER), the date designated as the cut-off date for data to be included in a PSUR/PBRER. For a periodic benefit-risk evaluation report (PBRER), the date designated as the cut-off date for data to be included in a PBRER, based on the international birth date. For a development safety update report (DSUR), the date is designated as the cut-off date for data to be included in a DSUR, based on the development international birth date. Date includes day and month (see ICH-E2F Guideline);

Development International Birth Date - means Date of first approval (or authorisation) for conducting an interventional clinical trial in any country;

Direct Healthcare Professional Communication - means communication intervention by which important safety information is delivered directly to individual healthcare professionals by MAH or the Authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicine or allied substance;

Falsified - means medical products that deliberately/fraudulently misrepresent their identity, composition or source;

Generic medicine or allied substance - means a medicine or allied substance which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicine or allied substance, and whose bioequivalence with the reference medicine or allied substance has been demonstrated by appropriate bioavailability studies;

Good Pharmacovigilance Practices - is a set of guidelines for the conduct of pharmacovigilance drawn up by the Authority, which apply to MAHs in the country;

Health Professional - has the meaning assigned to the words in the Health Professions Act, 2024 and includes a nurse or midwife registered under the Nurses and Midwives Act, 2019;

Herbal medicine or allied substance - means any medicine or allied substance, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations;

Identified Risk - means an untoward occurrence for which there is adequate evidence of an association with the medicine or allied substance of interest;

Individual Case Safety Report - format and content for the reporting of one or several suspected adverse reactions to a medicine or allied substance that occur in a single patient at a specific point of time. **Synonym Adverse (Drug) Reaction report;**

Inspection - the act by the Authority of conducting an official review of documents, facilities, records and any other resources that are deemed to be related to the safety monitoring system and that may be located at the site of the safety monitoring site, at the MAH and/or contracted party's facilities, or at other establishments deemed appropriate by the Authority;

International Birth Date - the date of the first Marketing Authorisation for any product containing the active substance granted to any company in any country in the world;

Investigational Medicine or allied substance (also referred to as investigational product - means a medicine or allied substance (including a placebo) being tested or used as a reference in a clinical trial, including a medicine or allied substance with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use;

Label - means any tag, brand, and mark, pictorial or other descriptive matter written, printed, brailled, marked, embossed or impressed on or attached to a container of any product;

Local Qualified Person for Pharmacovigilance - means a designated individual, resident in the Republic, employed and appointed by the MAH to implement the safety monitoring system on behalf of the Marketing Authorisation Holder in the country;

Marketing Authorisation Holder - means a person to whom a medicine or allied substance has been issued a marketing authorisation and is responsible for all aspects of the medicine or allied substances including quality, safety, efficacy, performance and compliance with conditions of marketing authorisation;

Medicine or allied substance - means any substance or combination of substances which may be administered to human beings or animals to make a medical diagnosis or to restore, correct or modify the physiological functions in human beings;

Minimum criteria for reporting - for the purpose of reporting cases of suspected adverse reactions, the minimum data elements for a case are an identifiable reporter, an identifiable patient, an adverse reaction and a suspect medicine or allied substance. See also Individual case safety report;

Missing information - gaps in knowledge about a medicine or allied substance, related to safety or use patient populations, which could be clinically significant;

Misuse - situations where the medicine or allied substance is intentionally and inappropriately used not in accordance with the authorised product information;

Newly identified signal - in periodic benefit-risk evaluation reports, a signal first identified during the reporting interval, prompting further actions or evaluation;

Non-interventional study - a study where the medicine or allied substance(s) is (are) prescribed in the usual manner;

Occupational exposure - means an exposure to a medicine or allied substance because of one's professional or non-professional occupation;

Off-label use - situation where a medicine or allied substance is intentionally used for a medicinal purpose not in accordance with the authorised product information. Off-label use includes use in non-authorised paediatric age categories;

Overdose - administration of a quantity of a medicine or allied substance given per administration or cumulatively which is

above the maximum recommended dose according to the authorised product information, Clinical judgment should always be applied;

Package leaflet - a leaflet containing information for the user which accompanies the medicine or allied substance;

Periodic Benefit Risk Evaluation Report - is 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;

Periodic Safety Update Report - is intended to provide an update of the worldwide safety experience of a medicinal product to the Authority at defined time points post authorisation. At these times, Marketing Authorisation 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;

Pharmacovigilance - science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. Synonym **Safety Monitoring, Vigilance.**

Pharmacovigilance System Master File - a detailed description of the Safety Monitoring System used by the MAH with respect to one or more authorised medicines and allied substances. Synonym **Safety Monitoring System Master File;**

Post-Authorisation Safety Study - any study relating to an authorised medicine or allied substance conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicine or allied substance, or of measuring the effectiveness of risk management measures. A post-authorisation safety study may be an interventional clinical trial or may follow an observational, non- interventional study design;

Potential - an untoward occurrence for which there is some basis for suspicion of an association with the medicine or allied substance of interest but where this association has not been confirmed;

Product Quality Complaint - any written, oral, or electronic communication that alleges a deficiency in the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of a medicine or allied substance after it has been released to the market;

Quality Management System - the organisational structure, responsibilities, procedures, processes and resources of the Safety Monitoring System as well as appropriate resource management, compliance management and record management. The quality management system is part of the Safety Monitoring System;

Reference Safety Information - in periodic benefit-risk evaluation reports for medicines and allied substances, all relevant safety information contained in the reference product information (e.g. the company core data sheet) prepared by the MAH and which the MAH is listed in the country. It is a subset of information contained within the MAH's reference product information for the periodic benefit-risk evaluation report. Where the reference product information is the company core data sheet, the reference safety information is the company core safety information;

Registry - an organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure;

Risk Management Plan - a detailed description of the risk management system. To this end, it must identify or characterise the safety profile of the medicine or allied substance(s) concerned, indicate how to characterise further the safety profile of the medicine or allied substance(s) concerned, document measures to prevent or minimise the risks associated with the medicine or allied substance, including an assessment of the effectiveness of those interventions and document post-authorisation obligations that have been imposed as a condition of the Marketing Authorisation;

Risk Management System - a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicine or allied substance, including the assessment of the effectiveness of those interventions;

Risk minimisation measure (Risk minimisation 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. These activities may consist of routine risk minimisation (e.g. product information) or additional risk minimization activities (e.g. healthcare professional or patient communications/educational materials);

Risks related to use of a medicine or allied substance - any risk relating to the quality, safety or efficacy of the medicine or allied substance as regards patients' health or public health and any risk of undesirable effects on the environment;

Safety concern - an important identified risk, important potential risk or missing information. It is noted that the ICH definition of safety concern is: an important identified risk, important potential risk or important missing information, i.e. includes the qualifier "important" in relation to missing information. The ICH-E2E Guideline uses the terms safety issue and safety concern interchangeably with the same definition for safety concern as defined in the ICH-E2C (R2) Guideline;

Safety Monitoring System - a system used by the MAH to fulfill the tasks and responsibilities and designed to monitor the safety of authorised medicines and allied substances and detect any change to their risk-benefit ratio benefit-risk balance;

Serious Adverse Reaction - an adverse reaction 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 defect. Life-threatening in this context refers to

a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (see ICH-E2D Guideline);

Signal - information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action;

Spontaneous report - unsolicited communication by a healthcare professional or consumer to a company, regulatory Authority or other organisation. Synonym: **Spontaneous notification;**

Substandard - also called "out of specification" are authorized medical products that fail to meet either their quality standards or specifications, or both;

Unexpected adverse reaction - an adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics. This includes class-related reactions which are mentioned in the summary of product

characteristics (SmPC) but which are not specifically described as occurring with this product. See also Summary of product characteristics;

VigiBase - the name of the WHO global ICSR database. It consists of reports of adverse reactions received from member countries.

1. INTRODUCTION

This guideline is issued by the Authority pursuant to Section 68 of the Act to monitor the safety of medicines and allied substances. The guideline describes obligations of the Marketing Authorisation Holders (MAHs) to set up a system for safety monitoring to collect, collate and evaluate information about suspected adverse reactions of medicines or allied substances it places on the Zambian market.

This guideline is intended to help all relevant stakeholders comply with the obligations for Safety Monitoring. It provides detailed guidance for MAHs on establishing and maintaining a safety monitoring system including its quality management, Safety Monitoring System Master File, adverse reaction/event reporting, risk management, post authorisation safety/efficacy studies, risk communication and safety monitoring inspection. The goal is to ensure that medicines and allied substances placed on the Zambian market are safe and effective and continue to provide a satisfactory balance between their benefit and risks.

This document is to be used in conjunction with other existing relevant laws and regulations. The good practices outlined below are to be considered general guides, and they may be adapted to meet individual needs if the MAH achieves

compliance with regulatory requirements. The Authority, in consultation with stakeholders, may from time to time amend any part of this guideline.

Objective

The purpose of this guideline is to ensure that Marketing Authorisation Holders comply with safety monitoring obligations. This guideline is in line with the Authority's mandate to ensure medicines being made available to the Zambians are safe and of good quality.

Scope

This guideline applies to MAHs, Local Responsible Persons, local distributors, individuals, public and private institutions, manufacturers and donors of medicines and allied substances. This guideline applies to all medicines and allied substances regulated by the Authority. The obligations concerned with the monitoring of adverse events or reactions occurring in clinical trials do not fall within the scope of this guideline.

2. SAFETY MONITORING SYSTEM

2.1. A holder of a marketing authorisation shall establish and maintain a safety monitoring (or Pharmacovigilance) system for a medicine or allied substance for receiving, managing, evaluating and reporting of adverse reactions or adverse events to a medicine or allied substance. The safety monitoring system shall be designed to monitor the safety of authorised medicines and allied substances and detect any change to their benefit-risk balance.

2.2. A safety monitoring system shall be characterised by its structures, processes and outcomes. It shall cover organisational structure, responsibilities, procedures, processes and resources of the safety monitoring system as well as appropriate resource management, compliance management and record management.

2.3. The safety monitoring system shall be adaptable to a public health emergency or animal disease emergency.

2.4. **Quality Management System (QMS)**

2.4.1. A holder of a marketing authorisation shall develop and maintain a quality management system for:

i. quality control, assurance and improvement of a safety monitoring system for a medicine or allied substance;
ii. ensuring continuous monitoring of safety monitoring data;
iii. submission of accurate data on adverse reactions or adverse events to the Authority; and
iv. communication of relevant safety information in relation to a medicine or allied substance to health professionals, veterinary surgeons or veterinary para-professionals and patients.

2.4.2. The overall objectives of the quality management system in the safety monitoring system are:

i. Complying with the legal requirements for pharmacovigilance tasks and responsibilities;
ii. Preventing harm from adverse reactions in humans arising from use of authorised medicines and allied substances within or outside the terms of marketing authorisation such as off-label use, misuse, abuse or medication errors which result in adverse reactions or from occupational exposure;
iii. Promoting the safe and effective use of medicines and allied substances, through providing timely information about the safety of medicines and allied

substances to patients, healthcare professionals and the public; and

iv. Contributing to the protection of patients and public health.

2.4.3. General Principles of QMS

With the aim of fulfilling the overall quality objectives, the following principles should guide the design of all structures and processes as well as the conduct of all tasks and responsibilities:

i. The needs of patients, healthcare professionals and the public in relation to the safety of medicines and allied substances should be met.

ii. Top management should provide leadership in the implementation of the quality management system and motivation for all staff members in relation to the quality objectives.

iii. All persons within the organisation should be involved in and support the safety monitoring system based on task ownership and responsibility to a degree according to their tasks and assigned responsibilities.

iv. All persons involved with the entire organisation should engage in continuous quality improvement.

v. Resources and tasks should be organised as structures and processes in a manner that will support the proactive, risk- proportionate, continuous and integrated conduct of pharmacovigilance.

vi. All available evidence on the benefit-risk balance of medicines and allied substances should be sought and all relevant aspects, which could impact on the benefit-risk balance and the use of a medicine or allied substance, should be considered for decision-making.

vii. Good cooperation should be fostered between MAHs, the Authority, public health organisations, patients, healthcare professionals, learned societies and other relevant bodies.

2.5. **Personnel**

2.5.1. Enough competent and appropriately qualified and trained personnel should be available for the performance of safety monitoring activities. Their responsibilities should include adherence to the defined principles.

2.5.2. Responsibilities of the safety monitoring personnel

Safety Monitoring Personnel with the support of the MAH shall be responsible for the effective oversight and implementation of pharmacovigilance activities including:

i. Ensuring that an effective pharmacovigilance system is established, implemented, maintained, and operated in accordance with applicable regulatory requirements and Good Pharmacovigilance Practices.

ii. Ensuring the timely collection, documentation, assessment, processing, and submission of Individual Case Safety Reports, including adverse drug reactions and other reportable safety information, within prescribed regulatory timelines.

iii. Monitoring the safety profile of medicinal products on an ongoing basis, identify and evaluate potential safety signals, and recommend appropriate risk-minimisation measures where necessary.

iv. Ensuring the preparation, review, and timely submission of required pharmacovigilance reports, including Periodic Safety Update Reports/Periodic

Benefit–Risk Evaluation Reports, Risk Management Plans, and other reports required by the Authority.

v. Serving as the designated pharmacovigilance contact with the Authority and ensuring timely responses to pharmacovigilance-related requests, inspections, and audits.

vi. Establishing and maintaining an effective pharmacovigilance quality system, including appropriate SOPs, documentation, record management, quality assurance, and implementation and monitoring of corrective and preventive actions, where applicable.

vii. Ensuring that personnel involved in pharmacovigilance activities receive appropriate initial and continuous training and are competent to perform their assigned responsibilities.

viii. Ensuring ongoing monitoring and evaluation of the benefit–risk profile of medicinal products and the timely communication of significant safety concerns to the Authority and other relevant stakeholders, as appropriate.

2.5.3. Responsibilities of Managerial staff

i. Ensuring that the organisation documents the quality management system as described in this section.

ii. Ensuring that the documents describing the quality management system are subject to document control in relation to their creation, revision, approval and implementation.

iii. Ensuring adequate record management.

iv. Reviewing the safety monitoring system including its quality management system at regular intervals in a risk- based manner to verify its effectiveness and introducing corrective and preventive measures where necessary.

v. Ensuring that mechanisms exist for timely and effective communication of safety concerns relating to medicines and allied substances within the organisation.

vi. Identifying and investigating concerns arising within the organisation regarding suspected non-adherence to the requirements of the quality management and safety monitoring systems and taking corrective and preventive action as necessary.

vii. Ensuring that audits are performed.

2.5.4. In relation to the management responsibilities described above, top management within the organisation should provide leadership through:

i. Ensuring that adequate resources are available and that training is provided;
ii. Ensuring that suitable and sufficient premises, facilities and equipment are available;
iii. Motivating all staff members based on shared values, trust and freedom to speak and act with responsibility and through recognition of staff members' contributions within the organisation;
iv. Assigning roles, responsibilities and authorities to staff members according to their competencies and communicating and implementing these throughout the organisation.

2.5.5. **Training personnel in safety monitoring**

i. Achieving the required quality for the conduct of safety monitoring 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 safety monitoring activities should receive initial training and annually thereafter. This training should relate to the roles and responsibilities of the personnel.

iii. Adequate training should also be provided for all staff members whom no specific safety monitoring tasks and responsibilities have been assigned but whose activities may have an impact on the Safety Monitoring System or the conduct of safety monitoring. Such activities include but are not limited to those related to clinical trials, product quality complaints, medicinal information, terminologies, sales and marketing, regulatory affairs, legal affairs and audits.

iv. The effectiveness of training must be assessed and records of this maintained.

v. The organisation should keep training plans and records for documenting, maintaining and developing the competences of personnel. Training plans should be based on training

needs assessment and should be subject to monitoring.

vi. 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.

vii. Appropriate instructions on the processes to be used in case of urgency (public health emergency, natural disasters, other health threats etc), including business continuity, should be provided by the organisation to their personnel.

2.6. Facilities and equipment for Safety Monitoring

2.6.1. Achieving the required quality for the conduct of safety monitoring processes and their outcomes is also intrinsically linked with appropriate facilities and equipment used to support the processes.

2.6.2. Facilities and equipment should include office space, information technology (IT) systems and (electronic) storage space.

2.6.3. Facilities and equipment should be located, designed, constructed, adapted and maintained to suit their intended purpose in line with the quality management system objectives for safety monitoring and be available for business continuity.

2.6.4. Facilities and equipment which are critical for the conduct of safety monitoring should be subject to appropriate checks, qualification and/or validation activities to prove their suitability and relevant records maintained.

2.6.5. There should be processes in place to keep awareness of the valid terminologies in their valid versions and to keep the IT systems up-to-date accordingly.

2.7. Specific quality management system procedures and processes

2.7.1. Compliance management by MAHs

For compliance management, MAHs should have specific quality management system procedures and processes in place to ensure the following:

i. The continuous monitoring of safety data, the examination of options for risk minimisation and prevention and that appropriate measures are taken by the MAH;

ii. The scientific evaluation of all information on the risks of medicines and allied substances as regards patients or public health, including adverse reactions arising from use of the medicine or allied substance within or outside the terms of its Marketing Authorisation;

iii. The submission of accurate and verifiable data on serious and non-serious adverse reactions to the Authority within the legally prescribed timeframes;

iv. The quality, integrity and completeness of the information submitted on the risks of medicines and allied substances, including processes to avoid duplicate submissions and to validate;

v. Effective communication by the MAH with the Authority, including:

   a) Communication on new or changed risks,

   b) The Safety Monitoring System Master File (see Section 3),

   c) Risk Management Systems (see Section 4),

   d) Risk minimisation measures (see Section 4),

   e) Periodic safety update reports (see Section 7),

f) Corrective and preventive actions (see Section 3 & 9) and

g) Post-authorisation safety studies (see Section 8).

vi. The update of product information by the MAH in the light of scientific knowledge;

vii. Appropriate communication of relevant safety information to healthcare professionals and patients (see Section 5).

2.8. **Record management**

2.8.1. The organisation should record all safety monitoring information and ensure that it is handled and stored to allow accurate reporting, interpretation and verification of that information.

2.8.2. A record management system should be put in place for all documents used for safety monitoring 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.

2.8.3. The record management system should support:

i. The management of the quality of safety monitoring 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 Safety Monitoring Systems and the conduct of safety monitoring activities for medicines and allied substances, in accordance with the applicable retention periods.

2.8.4. MAHs should 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 safety monitoring activities in conformity with the Data Protection laws.

2.8.5. As part of a record management system, specific measures should be taken at each stage in the storage and processing of safety monitoring data to ensure data security and confidentiality. This should involve strict limitation of access to documents and to databases to authorised personnel respecting the confidentiality of the data.

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

2.8.7. The record management system should be described in a record management policy.

2.9. Documentation of the quality management system

2.9.1. All elements, requirements and provisions adopted for the quality management system should be documented in a systematic and orderly manner in the form of written policies and procedures, such as quality plans, quality manuals and quality records and SOPs.

2.9.2. To have a systematic approach, the organisation should define in advance:

i. Quality objectives specific to the organisation in accordance with the overall quality objectives; and

ii. Methods for monitoring the effectiveness of the Safety Monitoring System.

iii. The documentation of the quality management system should include:

a) Documents on organogram and assignments of tasks to personnel;

b) Training plans and records which should be kept and made available for audit and inspection;

c) Instructions for the compliance management processes;

d) Appropriate instructions on the processes to be used in case of urgency, including business continuity;

e) Performance indicators used to continuously monitor the good performance of safety monitoring activities;

f) Reports on quality audits and follow-up audits, including their dates and results;

g) The methods of monitoring the efficient operation of the quality management system and its ability to fulfil the quality objectives;

h) A record management policy;

i) Records generated through safety monitoring processes that demonstrate key procedural steps have been completed;

j) Records and reports relating to the facilities and equipment including functionality checks, qualification and validation activities which demonstrate that all steps required by the

applicable requirements, protocols and procedures have been taken;

k) Records demonstrate that deficiencies and deviations from the established quality management system are monitored, that corrective and preventive actions have been taken, that solutions have been applied to deviations or deficiencies, and that the effectiveness of the actions taken has been verified.

2.10. Additional quality management system documentation

2.10.1. In addition to the quality management system documentation, MAH should document:

i. The human resource management in the Safety Monitoring System Master File (PSMF);

ii. Job descriptions defining the duties of everyone involved in safety monitoring including the managerial and supervisory staff;

iii. An organisational chart defining the hierarchical relationships of managerial and supervisory staff;

iv. Instructions on critical processes in the Safety Monitoring System Master File (PSMF); and

v. The record management system in the Safety Monitoring System Master File (PSMF);

vi. Organisational structures and assignments of tasks, responsibilities and authorities to all personnel directly involved in safety monitoring tasks.

2.10.2. The Marketing Authorisation Holder shall put in place the quality system processes for ensuring:

i. The retention of minimum elements of the Safety Monitoring System Master File (PSMF) if the system described in the PSMF exists and for at least a further 5 years after it has been formally terminated by the marketing authorisation holder;

ii. The retention of safety monitoring data and documents relating to individual authorised medicinal products if the marketing authorisation exists and for at least a further 10 years after the marketing authorisation has ceased to exist.

iii. The retention of safety monitoring data and documents relating to Advanced Therapy Medicinal Products (ATMP) if the marketing authorisation exists and for at least a further 30 years after the marketing authorisation has ceased to exist.

2.11. Critical safety monitoring processes and business Continuity

2.11.1. The following safety monitoring processes should be considered critical:

i. Continuous safety profile monitoring and benefit-risk evaluation of authorised medicines and allied substances;

ii. Establishing, assessing and implementing risk management systems and evaluating the effectiveness of risk minimisation measures;

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

iv. Signal detection and management;

v. Scheduling, preparation (including data evaluation and quality control), submission and assessment of periodic safety update reports;

vi. Meeting commitments and responding to requests from the Authority, including provision of correct and complete information;

vii. Interaction between the safety monitoring and product quality defect systems;

viii. Communication about safety concerns between the MAH and the Authority, in particular notifying changes to the risk-benefit ratio of a medicine or allied substance;

ix. Communicating information to patients and healthcare professionals about changes to benefit-risk balance of medicines and allied substances for the purpose of safe and effective use of medicines and allied substances;

x. Keeping product information up to date with the current scientific knowledge, including conclusions of assessment and recommendations from the Authority;

xi. Implementation of variations to marketing authorisation for safety reasons according to the urgency required.

2.11.2. Business continuity plans should be established in a risk-based manner and should include:

i. Provisions for events that could severely impact on the organisation's staff and infrastructure in general or on the structures and processes for safety monitoring in particular; and

ii. Back-up systems for urgent exchange of information within an organisation, amongst organisations sharing safety monitoring tasks as well as between the MAH and the Authority.

2.12. Monitoring the Safety Monitoring System and its quality management system

2.12.1. Processes to monitor the performance and effectiveness of a Safety Monitoring System and its quality management system should include:

i. Reviews of the systems by those responsible for management;
ii. Review of audit and inspection findings;
iii. Compliance monitoring;
iv. Evaluating the effectiveness of actions taken with medicines and allied substances for the purpose of minimising risks and supporting their safe and effective use in patients.

2.12.2. The organisation should use performance indicators to continuously monitor the good performance of safety monitoring activities in relation to the quality requirements.

2.12.3. The adequacy of the requirements for the quality management system should be monitored by

managerial staff, who should review the documentation of the quality management system at regular intervals, with the frequency and the extent of the reviews to be determined in line with the provisions of these guidelines in a risk-based manner. Pre-defined programmes for the review of the system should therefore be in place.

2.12.4. Reviews of the quality management system should include a review of standard operating procedures and work instructions, deviations from the established quality management system, audit and inspection reports as well as the use of the indicators referred to above.

2.12.5. Risk-based audits of the quality management system should be performed at regular intervals to ensure that it complies with the requirements for the quality management system, the human resource management, the compliance management, the record management and the data retention and to ensure its effectiveness.

2.12.6. Audits of the quality management system should include audit of the Safety Monitoring System, which is the subject of the quality management system. The methods and processes for the audits are described in Section 9.

2.12.7. In relation to the Safety Monitoring System of the MAH, a report should be drawn up on the results for each quality audit and any follow-up audits be sent to the management responsible for the matters audited.

2.12.8. The report should include the results of audits of organisations or persons the MAH has delegated tasks to, as these are part of the MAH's Safety Monitoring System.

2.12.9. Because of the monitoring of the performance and effectiveness of a Safety Monitoring System and its quality management system (including the use of audits), corrective and preventive measures should be implemented when deemed necessary. In particular, because of audits, corrective action(s), including a follow-up audit of deficiencies, should be taken where necessary.

2.13. Qualified Person for Pharmacovigilance (LQPPV)

2.13.1. The MAH shall, as part of the Safety Monitoring System, permanently and continuously have at its disposal a local qualified person for pharmacovigilance (LQPPV) responsible for safety

monitoring of a medicine or allied substance on behalf of the MAH.

2.13.2. The MAH should submit the name and contact details of the local QPPV to the Authority.

2.13.3. The duties of the local QPPV should be defined in a job description.

2.13.4. The hierarchical relationship of the local QPPV should be defined in an organisational chart together with those of other managerial and supervisory staff.

2.13.5. Information relating to the local QPPV should be included in the Safety Monitoring System Master File.

2.13.6. Each Safety Monitoring System can have only one local QPPV.

2.13.7. A person shall not be engaged as a local QPPV by more than one MAH at the same time.

2.13.8. The Authority may waive the requirements in 2.13.6 and 2.13.7 where the safety monitoring systems belong to the same MAH or the MAHs have a shared safety monitoring system, and the Authority is satisfied that the local QPPV has adequate capacity, resources, and support to meet every obligation without being overburdened.

2.13.9. The MAH should ensure that the local QPPV has sufficient Authority to influence the performance of

the quality management system and the safety monitoring activities of the MAH.

2.13.10. The MAH should ensure that the local QPPV has access to the Safety Monitoring System Master File as well as Authority over it and is notified of any changes to it.

2.13.11. The Authority over the Safety Monitoring System and the Safety Monitoring System Master File should allow the local QPPV to implement changes to the system and provide input into Risk Management Plans as well as the preparation of regulatory action in response to emerging safety concerns.

2.13.12. Overall, the MAH should ensure that structures and processes are in place, so that the local QPPV can fulfil their responsibilities. To do this, the MAH should ensure that mechanisms are in place so that the local QPPV receives all relevant information and that the local QPPV can access all information the local QPPV considers relevant, on:

i. safety concerns and any other information relating to the benefit-risk evaluation of the medicine or allied substance covered by the Safety Monitoring System;

ii. Ongoing or completed clinical trials and other studies the MAH is aware of, and which may be relevant to the safety of the medicine or allied substance;

iii. Information from sources other than from the specific MAH, e.g. from those with whom the MAH has contractual arrangements; and

iv. The procedures relevant to safety monitoring which the MAH has in place at every level to ensure consistency and compliance across the organisation.

2.13.13. The outcome of the regular reviews of the quality management system referred to in and the measures introduced should be communicated by the managerial staff to the local QPPV.

2.13.14. Compliance information should be provided to the local QPPV periodically. Such information may also be used to assure the local QPPV that commitments in the framework of risk management plans and post-authorisation safety systems are being adhered to.

2.13.15. The managerial staff should also inform the local QPPV of scheduled safety monitoring audits. The local QPPV should be able to trigger an audit where appropriate. The managerial staff should provide

the local QPPV with a copy of the corrective and preventive action plan following each audit relevant to the Safety Monitoring System that the local QPPV is responsible for, so that the local QPPV can ensure that appropriate corrective actions are implemented.

2.13.16. Regarding its adverse reaction database (or other systems to collate adverse reaction reports), the MAH should implement a procedure to ensure that the local QPPV can obtain information from the database, for example, to respond to urgent requests for information from the Authority, at any time. If this procedure requires the involvement of other personnel, for example, database specialists, then this should be considered in the arrangements made by the MAH for supporting the local QPPV outside of normal working hours.

2.13.17. When MAH intends to expand its product portfolio, for example, by acquisition of another company or by purchasing individual medicines or allied substances from another MAH, the local QPPV should be notified as early as possible in due diligence process in order that the potential impact on Safety Monitoring System can be assessed and the system be adapted accordingly.

2.13.18. The local QPPV may also have a role in determining what safety monitoring data should be requested from the other company, either pre- or post-acquisition. In this situation, the local QPPV should be made aware of the sections of the contractual arrangements that relate to responsibilities for safety monitoring activities and safety data exchange and have the Authority to request amendments.

2.13.19. When MAH intends to establish a partnership with another MAH, organisation or person that has a direct or indirect impact on the Safety Monitoring System, the local QPPV should be informed early enough and be involved in the preparation of the corresponding contractual arrangements so that all necessary provisions relevant to the Safety Monitoring System are included.

2.14. Qualifications and training of the qualified local person responsible for pharmacovigilance

2.14.1. The local QPPV shall:

i. Have a degree in Pharmacy, Clinical Pharmacy, Pharmacology, Clinical Pharmacology, Pharmaceutical Sciences, Medicine, or other related health fields;

ii. Postgraduate diploma/degree in Pharmacovigilance as an added advantage;

iii. Have adequate theoretical knowledge and practical experience in pharmacovigilance;

iv. Have practical skills for the management of pharmacovigilance systems;

v. Be a natural person resident, operating and appropriately licensed to practice in Zambia.

2.14.2. The MAH should provide the local QPPV with training in relation to its Safety Monitoring System, which is appropriate for the role prior to the local QPPV taking up the position and which is appropriately documented. Consideration should be given to additional training, as needed, of the local QPPV in the medicines and allied substances covered by the Safety Monitoring System.

2.14.3. **Roles and responsibilities of the local QPPV**

i. The local qualified person responsible for safety monitoring shall be at the MAH's disposal permanently and continuously. Back-up arrangements in the case of absence of the local QPPV should be in place and should be provided with the local QPPV's contact details. The local

QPPV should ensure that the back-up person has all necessary information to fulfil the role. The local QPPV should have expertise or access to expertise in relevant areas such as toxicology, medicine, pharmaceutical sciences, epidemiology and biostatistics.

ii. The local QPPV should be responsible for the establishment and maintenance of the MAH's Safety Monitoring System and therefore should have sufficient Authority to influence the performance of the quality management system and the safety monitoring activities and to promote, maintain and improve compliance with the legal requirements. Hence, the local QPPV should have access to the Safety Monitoring System Master File and be in a position of Authority to ensure and to verify that the information contained in the Safety Monitoring System Master File is an accurate and up-to-date reflection of the Safety Monitoring System under the local QPPV's responsibility.

iii. In relation to the medicines and allied substances covered by the Safety Monitoring System, specific additional responsibilities of the local QPPV should include:

a) Having an overview of medicine or allied substance safety profiles and any emerging safety concerns;
b) Being aware of any conditions or obligations adopted as part of the marketing authorisation and other commitments relating to safety or the safe use of the product;
c) Being aware of risk minimisation measures;
d) Being involved in the review and sign-off of protocols of post- authorisation safety studies to be conducted in Zambia;
e) Being aware of post-authorisation safety studies requested by the Authority including the results of such studies;
f) Providing input into risk management plans;
g) Ensuring conduct of safety monitoring and submission of all safety monitoring-related documents in accordance with the legal requirements and this guideline;
h) Ensuring the necessary quality, including the correctness and completeness, of safety monitoring data submitted to the Authority;
i) Ensuring full and prompt response to any request from the Authority for the provision of additional information necessary for the

evaluation of the benefits and risks of a medicine or allied substance;

j) Providing any other information relevant to the benefit-risk evaluation as may be requested by the Authority;

k) Providing input into the preparation of regulatory action in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and communication to patients and healthcare professionals);

l) Acting as a single safety contact point for the Authority.

iv. This responsibility for the Safety Monitoring System means that the local QPPV has oversight over the functioning of the system in all relevant aspects, including its quality management system (e.g. standard operating procedures, contractual arrangements, database operations, compliance data regarding quality, completeness and timeliness of expedited reporting and submission of periodic update reports, audit reports and training of personnel in relation to safety monitoring).

v. The local QPPV should be aware of the validation status of the adverse reaction database if applicable, including any failures that occurred during

validation and the corrective actions that have been taken to address the failures. The local QPPV should also be informed of significant changes that are made to the database (e.g. changes that could have an impact on safety monitoring activities).

vi. The local QPPV may delegate specific tasks, under supervision, to appropriately qualified and trained individuals, for example, acting as safety experts for certain products, provided that the local QPPV maintains system oversight and overview of the safety profiles of all medicines and allied substances. Such delegation should be documented.

2.15. Tasks subcontracted by the MAH

2.15.1. MAH may subcontract certain activities of the Safety Monitoring System to third parties. However, the role of the local QPPV shall not be subcontracted.

2.15.2. The MAH should nevertheless retain full responsibility for the completeness and accuracy of the Safety Monitoring System Master File. The ultimate responsibility for the fulfilment of all safety monitoring tasks and responsibilities as well as the quality and

integrity of the Safety Monitoring System always remain with the MAH.

2.15.3. Where the MAH has sub-contracted some of its safety monitoring tasks, it should retain responsibility for ensuring that an effective quality management system is applied in relation to those tasks. All guidance provided in this guideline is also applicable to the other organisation to which the tasks have been subcontracted.

2.15.4. When subcontracting tasks to another organisation, the MAH should draw up subcontracts and these should be detailed, up-to-date and clearly document the contractual arrangements between the MAH and the other organisation, describing arrangements for delegation and the responsibilities of each party.

2.15.5. A description of the subcontracted activities and/or services should be included in the Safety Monitoring System Master File (Section 3) and a list of the subcontracts should be included in an annex to the Safety Monitoring System Master File, specifying the product(s) organisation may be subject to inspection at the discretion of the Authority.

2.15.6. Contractual arrangements should be prepared with the aim of enabling compliance with the legal requirements by each party involved. When preparing contractual arrangements, the MAH should include sufficiently detailed descriptions of the delegated tasks, the related interactions and data exchange, together with, for example, agreed definitions, tools, assignments and timelines.

2.15.7. The contractual arrangements should also contain clear information on the practical management of safety monitoring as well as related processes, including those for the maintenance of safety monitoring databases. Further, they should indicate which processes are in place to check whether the agreed arrangements are being adhered to on an ongoing basis. In this respect, regular risk-based audits of the other organisation by the MAH or introduction of other methods of control and assessment are recommended.

3. SAFETY MONITORING SYSTEM MASTER FILE

3.1. The Safety Monitoring System Master File provides an overview of the Safety Monitoring System put in place by the MAH and contributes to the appropriate management of and improvement(s) to the Safety Monitoring System. The Safety Monitoring System Master File enables the MAH and local QPPV to:

a) Gain assurance that a Safety Monitoring System has been implemented in accordance with the requirements;
b) Confirm aspects of compliance in relation to the system;
c) Obtain information about deficiencies in the system, or non-compliance with the requirements;
d) Obtain information about risks or actual failure in the conduct of specific aspects of pharmacovigilance.

3.2. Maintenance of Safety Monitoring System Master File

3.2.1. MAHs are required to maintain a Safety Monitoring System Master File and submit to the Authority during application for Marketing Authorisation of a medicine or allied substance, summary information about the Safety Monitoring System, including information on

the location of the Safety Monitoring System Master File.

3.2.2. The Safety Monitoring System Master File should be continuously accessible to the qualified person responsible for pharmacovigilance in Zambia.

3.3. Transfer of responsibility for the PSMF

3.3.1. Transfer or delegation of responsibilities and activities concerning the Master File should be documented and managed to ensure that the MAH fulfils their responsibilities. Since a specific local QPPV has responsibility for the Safety Monitoring System, changes to the Safety Monitoring System Master File should also be notified to the local QPPV to support their Authority to make improvements to the system. The types of changes that should be routinely and promptly notified to the local QPPV are:

i. The addition of corrective and/or preventive actions to the Safety Monitoring System Master File (e.g. following audits and inspections). The local QPPV should also be able to access information about deviations from the processes defined in the quality management system for safety monitoring;

ii. Changes to content that fulfil the criteria for appropriate oversight of the Safety Monitoring

System (in terms of capacity, functioning and compliance);

iii. Transfer of significant services for safety monitoring to a third party (e.g. outsourcing of PSUR/PBRER production);

iv. Inclusion of products into the Safety Monitoring System for which the local QPPV is responsible;

v. Changes for existing products which may require a change or increased workload in relation to safety monitoring activity e.g. new indications or studies;

vi. Any other updates to the Safety Monitoring System Master File.

3.3.2. Any recipient local QPPV should explicitly accept the transfer of responsibility for a Safety Monitoring System in writing. The local QPPV should be able to ensure and to verify that the information contained in the Safety Monitoring System Master File is an accurate and up to date reflection of the Safety Monitoring System under his/her responsibility.

3.4. The representation of Safety Monitoring Systems

3.4.1. The Safety Monitoring System Master File shall describe the Safety Monitoring System for one or more medicines and allied substances of the MAH. For different categories of medicines and allied substances,

the MAH may, if appropriate, apply separate Safety Monitoring Systems. Each such system should be described in a separate Safety Monitoring System Master File. Those files should cumulatively cover all medicines and allied substances of the MAH for which a Marketing Authorisation has been issued.

3.4.2. It is anticipated that there will be circumstances where a single MAH may establish more than one Safety Monitoring System e.g. specific system for types of products (vaccines, consumer health, etc.), or that the Safety Monitoring System may include products from more than one MAH. In either case, a single and specific Master File shall be in place for each system.

3.4.3. A single local QPPV should be appointed to be responsible for the establishment and maintenance of the Safety Monitoring System as described in the Master File.

3.4.4. For a particular medicine or allied substance, the MAH may delegate through written agreement (e.g. to a licensing partner or contractor) part of the safety monitoring activities for which the MAH is responsible.

3.4.5. Where safety monitoring activities have been subcontracted, the appointment of the local QPPV shall remain with the MAH. Where applicable, a list of all Safety Monitoring System Master Files held by the

same MAH should be provided in the annex; this includes:

i. Their location(s);

ii. Details of the responsible local QPPV(s); and

iii. The relevant medicines or allied substances.

3.4.6. When delegating any activities concerning the Safety Monitoring System and its Master File, the MAH retains ultimate responsibility for the Safety Monitoring System, submission of information about the Safety Monitoring System Master File location, maintenance of the Safety Monitoring System Master File and its provision to the Authority. Detailed written agreements describing the roles and responsibilities for Safety Monitoring System Master File content, submissions and management, as well as to govern the conduct of safety monitoring in accordance with the legal requirements, should be in place.

3.5. Content of a Safety Monitoring System Master File (PSMF)

3.5.1. The Safety Monitoring System Master File should include documents to describe the Safety Monitoring System. The content of the Safety Monitoring System Master File should be as outlined in this section and

should reflect the global availability of safety information for medicines and allied substances authorised in Zambia. The content should be indexed to allow for efficient navigation around the document.

3.5.2. The main principle for the structure of the content of the Safety Monitoring System Master File is that the primary topic sections contain information that is fundamental to the description of Safety Monitoring System. Detailed information is required to fully describe the system, and, since this may change frequently, it should be referred to and contained in the Annexes.

3.6. Qualified person responsible for pharmacovigilance (LQPPV)

3.6.1. The information relating to the local QPPV provided in the PSMF should include:

i. A description of the responsibilities guaranteeing that the qualified person has sufficient Authority over the Safety Monitoring System to promote, maintain and improve compliance;

ii. A summary curriculum vitae with the key information on the role of the qualified person responsible for pharmacovigilance;

iii. Contact details;

iv. Details of back-up arrangements to apply in the absence of the qualified person responsible for pharmacovigilance;

v. Evidence of training relevant to safety monitoring;

vi. A list of tasks that have been delegated by the qualified person for pharmacovigilance should also be included in the Annexes. This should outline the activities that are delegated and to whom and include access to a medicinally qualified person if applicable. This list may be supplied as a copy of a written procedural document provided the required content is covered.

vii. The details provided in relation to the local QPPV should also include the description of the local QPPV qualifications, experience and training relevant to safety monitoring. The contact details supplied should include name, postal, telephone, and e-mail and represent the usual working address of the local QPPV, which may therefore be different to the MAH address.

3.7. Organisational structure of the MAH

3.7.1. A description of the organisational structure of the MAH relevant to the Safety Monitoring System must be provided. The description should provide a clear

overview of the company(ies) involved, the main safety monitoring departments and the relationship(s) between organisations and operational units relevant to the fulfilment of safety monitoring obligations. This should include third parties. Specifically, the Safety Monitoring System Master File should describe:

i. The organisational structure of the MAH(s), showing the position of the local QPPV in the organisation.

ii. The site(s) where the safety monitoring functions are undertaken covering individual case safety report collection, evaluation, safety database case entry, periodic safety update report production, signal detection and analysis, management of the risk management plan, pre- and post-authorisation study management, and management of safety variations to product particulars.

iii. Flow charts may be particularly useful; the name of the department or third party should be indicated.

3.8. Delegated activities

3.8.1. The Safety Monitoring System Master File, where applicable, should contain a description of the delegated activities and/or services relating to the

fulfillment of safety monitoring obligations. This includes arrangements with other parties in any country, worldwide and if applicable, to the Safety Monitoring System applied to products authorised in Zambia.

3.8.2. Links with other organisations, such as co-marketing agreements and contracting safety monitoring activities, should be outlined. A description of the location and nature of contracts and agreements relating to the fulfilment of safety monitoring obligations should be provided. This may be in the form of a list/table to show the parties involved, the roles undertaken and the product(s) concerned. The list should be organised according to; service providers (e.g. medicinal information, auditors, patient support programme providers, study data management etc.), commercial arrangements (distributors, licensing partners, co-marketing etc.) and other technical providers (hosting of computer systems etc.)

3.9. Sources of safety data

3.9.1. The description of the main units for safety data collection should include all parties responsible on a global basis for solicited and spontaneous case

collection for products authorized in Zambia. This should include medicinal information sites as well as affiliate offices and may take the form of a list describing the country, nature of the activity, and the product(s) (if the activity is product specific) and providing a contact point (address, telephone and email) for the site. The list may be in the annexes of the PSMF. The information about third parties (licensed partners or local distribution/marketing arrangements) should also be included in the section describing contracts and agreements.

3.9.2. Flow diagrams indicating the main stages, time frames and parties involved may be used. However, the description of the process for ICSRs from receipt to reporting to the Authority should indicate the department and/or third parties involved.

3.9.3. Sources may include data arising from study sources, including any studies, registries, surveillance or support programs sponsored by the MAH through which ICSRs could be reported. The MAH should be able to produce and make available a list of such sources to support inspection, audit and local QPPV oversight.

3.9.4. The list should describe on a worldwide basis the status of each study/program, the applicable country(ies), the product(s), and the main objective. It should distinguish

between interventional and non- interventional studies and should be organized by active substance. The list should be comprehensive for all studies/programs and should include on-going studies/programs as well as studies/programs completed in the last 2 years and may be in an annex or provided separately.

3.10. Computerised systems and databases

3.10.1. The location, functionality and operational responsibility for computerized systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose should be described in the Safety Monitoring System Master File.

3.10.2. Where multiple computerized systems/databases are used, the applicability of these to safety monitoring activities should be described in such a way that a clear overview of the extent of computerization within the Safety Monitoring System can be understood.

3.10.3. The validation status of key aspects of the computer system functionality should also be described; the change control, nature of testing, back-up procedures and electronic data repositories vital to safety monitoring compliance should be included in summary,

and the nature of the available documentation described.

3.10.4. For paper-based system (where an electronic system may only be used for expedited submission of ICSRs), the management of the data, and mechanisms used to assure the integrity and accessibility of the safety data, and in particular, the collation of information about adverse drug reactions/ adverse event should be described.

3.11. Safety Monitoring processes

3.11.1. An essential element of any Safety Monitoring System is that there are clear written procedures in place. Section 2 describes the required minimum set of written procedures for safety monitoring. A description of the procedural documentation available (standard operating procedures, manuals, etc.), the nature of the data held (e.g. the type of case data retained for ICSRs) and an indication of how records are held (e.g. safety database, paper file at site of receipt) should be provided in the Safety Monitoring System Master File.

3.11.2. A description of the process, data handling and records for the performance of safety monitoring, covering the following aspects, should be included in the Safety Monitoring System Master File:

i. Continuous monitoring of product benefit-risk profile(s) applied and the result of evaluation and the decision-making process for taking appropriate measures; this should include signal generation, detection and evaluation. This may also include several written procedures and instructions concerning safety database outputs, interactions with clinical departments etc.;

ii. Risk management system(s) and monitoring of the outcome of risk minimisation measures; several departments may be involved in this area, and interactions should be defined in written procedures or agreements;

iii. ICSR collection, collation, follow-up, assessment and reporting; the procedures applied to this area should clarify what are local and what are global activities;

iv. PSUR/PBRER scheduling, production and submission, if applicable;

v. Communication of safety concerns to consumers, healthcare professionals and the Authority;

vi. Implementation of safety variations to the summary of product characteristics (SmPC) and patient information leaflets; procedures should cover both internal and external communications.

3.11.3. In each area, the MAH should be able to provide evidence of a system that supports appropriate and timely decision making and action.

3.11.4. The description must be accompanied by the list of processes for compliance management as well as interfaces with other functions. Interfaces with other functions include, but are not limited to, the roles and responsibilities of the local QPPV, responding to requests for information by the Authority, literature searching, safety database change control, safety data exchange agreements, safety data archiving, pharmacovigilance auditing, and quality control and training.

3.11.5. The list, which may be in the Annexes, should comprise the procedural document reference number, title, effective date and document type (for all standard operating procedures, work instructions, manuals etc.). Procedures belonging to service providers and other third parties should be clearly identified.

3.12. Safety Monitoring System performance

3.12.1. The Safety Monitoring System Master File should contain evidence of the ongoing monitoring of performance of the Safety Monitoring System including compliance of the main outputs of safety

monitoring. The Safety Monitoring System Master File should include a description of the monitoring methods applied and contain as a minimum:

i. An explanation of how the correct reporting of ICSRs is assessed. In the annex, figures/graphs should be provided to show the timeliness of 15-day and 30-day reporting over the past year;

ii. A description of any metrics used to monitor the quality of submissions and performance of safety monitoring. This should include information provided by the Authority regarding the quality of ICSR reporting, PSUR/PBRERs or other submissions;

iii. An overview of the timeliness of PSUR/PBRER reporting to the Authority (the annex should reflect the latest figures used by the MAH to assess compliance);

iv. An overview of the methods used to ensure timeliness of safety variation submissions including the tracking of required safety variations that have been identified but not yet been submitted;

v. Where applicable, an overview of adherence to risk management plan commitments, or other obligations or conditions of Marketing Authorisation(s) relevant to safety monitoring.

3.12.2. Targets for the performance of the Safety Monitoring System should be described and explained.

3.12.3. A list of performance indicators must be provided in the Annex to the Safety Monitoring System Master File, alongside the results of (actual) performance measurements.

3.13. Quality Management System

A description of the quality management system should be provided, in terms of the structure of the organisation and the application of the quality to safety monitoring. This should include:

3.13.1. Document and Record Control

i. A description of the archiving arrangements for electronic and/or hardcopy versions of the Safety Monitoring System Master File should be provided, as well as an overview of the procedures applied to other quality management systems and safety monitoring records and documents.

ii. A general description of the types of documents used in safety monitoring (standards operating procedures, work instructions etc.), the applicability of the various documents at global, regional or local level within the organisation, and the controls that are applied to their accessibility, implementation and maintenance.

iii. Information about the documentation systems applied to relevant procedural documents under the control of third parties.

iv. A list of specific procedures and processes related to the safety monitoring activities and interfaces with other functions, with details of how the procedures can be accessed must be provided, and detailed guidance for their inclusion.

3.13.2. Training

A description of the resource management for the performance of safety monitoring activities:

i. The organisational chart indicating the number of people (full-time equivalents) involved in safety monitoring activities, which may be provided in the section describing the organisational structure.

ii. Information about sites where the personnel are located whereby the sites are provided in the PSMF in relation to the organisation of specific safety monitoring activities and in the Annexes which provide the list of site contacts for sources of safety data. However, a description should be provided to explain the training organisation in relation to the personnel and site information;

iii. A summary description of the training concept, including a reference to the location of training files.

iv. Staff should be appropriately trained in performing safety monitoring related activities and this includes not only staff within safety monitoring departments but also any individual that may receive or handle safety reports.

3.13.3. Auditing

i. Information about quality assurance auditing of the Safety Monitoring System should be included in the Safety Monitoring System Master File.

ii. A description of the approach used to plan audits of the Safety Monitoring System and the reporting mechanism and timelines should be provided, with a current list of the scheduled and completed audits concerning the Safety Monitoring System maintained in the annex. This list should describe the date(s) (of conduct and of report), scope and completion status of audits of service providers, specific safety monitoring activities or sites undertaking safety monitoring and their operational interfaces relevant to the fulfilment of the obligations in the regulations and cover a period of 5 years.

iii. The Safety Monitoring System Master File should also contain a note associated with any audit where significant findings are raised.

iv. The audit report must be documented within the quality management system; in the Safety Monitoring System Master File it is sufficient to provide a brief description of the corrective and/or preventive action(s) associated with the significant finding, the date it was identified and the anticipated resolution date(s), with cross reference to the audit report and the documented corrective and preventive action plan(s).

v. In the annex, in the list of audits conducted, those associated with unresolved notes in the Safety Monitoring System Master File, should be identified. The note and associated corrective and preventive action(s), should be documented in the Safety Monitoring System Master File until the corrective and/or preventive action(s) have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently verified. The addition, amendment or removal of the notes must therefore be recorded in the amendment log.

vi. As a means of managing the Safety Monitoring System, and providing a basis for audit or inspection, the Safety Monitoring System Master File should also describe the

process for recording, managing and resolving deviations from the quality management system. The Master File should also document deviations from safety monitoring procedures, their impact and management until resolved. This may be documented in the form of a list referencing a deviation report, and its date and procedure concerned.

3.14. Annex to the PSMF

3.14.1. An annex to the Safety Monitoring System Master File should contain the following documents:

i. A list of medicines and allied substances covered by the Safety Monitoring System Master File including the name of the medicine or allied substance, the name of the active substance(s) and the corresponding MA number.

ii. The list should be organised per active substance and, where applicable, should indicate what type of product specific safety monitoring requirements exist (for example risk minimisation measures contained in the risk management plan or laid down as conditions of the Marketing Authorisation, non-standard PSUR/PBRER periodicity. The monitoring information may be provided as a secondary list.

iii. For Products that are included in a different Safety Monitoring System, for example, because the MAH

has more than one Safety Monitoring System or third party agreements exist to delegate the system, reference to the additional Safety Monitoring System Master File(s) should also be provided as a separate list in the Annexes, such that, for MAH, the entire product portfolio can be related to the set of Safety Monitoring System Master Files.

iv. Where Safety Monitoring Systems are shared, all products that utilise the Safety Monitoring System should be included, so that the entire list of products covered by the file is available. The product lists may be presented separately, organised by MAH. Alternatively, a single list may be used, which is supplemented with the name of the MAH(s) for each product, or a separate note can be included to describe the product(s) and the MAH(s) covered;

v. A list of written policies and procedures;

vi. A list of contractual agreements covering delegated activities including the medicines and allied substances;

vii. A list of tasks that have been delegated by the qualified person for pharmacovigilance;

viii. A list of all completed audits, for a period of five years, and a list of audit schedules;

ix. Where applicable, a list of performance indicators;

x. Where applicable, a list of other Safety Monitoring System Master Files held by the same MAH. This list should include the Safety Monitoring System Master File number(s), the name of MAH and of the local QPPV responsible for the Safety Monitoring System. If the Safety Monitoring System is managed by another party that is not MAH, the name of the service provider should also be included;

xi. A logbook and other change control documentation should be included as appropriate. Documented changes should include at least the date, person responsible for the change and the nature of the change.

3.15. Change control, amendment logs, versions and archiving

3.15.1. It is necessary for MAHs to implement change control systems and to have robust processes in place to continuously be informed of relevant changes to maintain the Safety Monitoring System Master File accordingly. The Authority may request information about important changes to the Safety Monitoring System, such as, but not limited to:

i. Changes to the safety monitoring 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;

ii. Changes in the provision of significant services for safety monitoring, especially major contractual arrangements concerning the reporting of safety data;

iii. Organisational changes, such as takeovers, mergers, the sites at which safety monitoring is conducted or the delegation/transfer of Safety Monitoring System Master File management.

3.15.2. In addition to these changes being documented in the Safety Monitoring System Master File for the purpose of change control (in the amendment log), the local QPPV should always be kept informed of these changes.

3.15.3. Changes to the Safety Monitoring System Master File should be recorded, such that a history of changes is available (specifying the date and the nature of the change), changes to the PSMF must be recorded in the amendment log. Descriptive changes to the content of the Master File must be recorded in the amendment log.

3.15.4. Change history for the information contained in the annexes may be 'on demand', in which case the logbook would indicate the date of the revision of PSMF content and/or annex update(s), the history of changes for annex content would also be updated. Information that is being regularly updated and is contained in the annexes, such as product and standard operating procedure lists or compliance figures, may include output from controlled systems (such as electronic document management systems or regulatory databases). The superseded versions of such content may be managed outside of the Safety Monitoring System Master File content itself, provided that the history of changes is maintained and available to the Authority on request. If the Safety Monitoring System Master File has not been requested, or has remained unchanged for a period of time (for example, if the changes in the content of annexes are managed outside of the Safety Monitoring System Master File), it is recommended that a review is conducted periodically. MAHs need to ensure that the obligations concerning the timely provision of the Safety Monitoring System Master File can be met. It is also noted that the local QPPV must be able to gain access to current and accurate information about the Safety Monitoring System, hence permanent and

continuous access to the Safety Monitoring System Master File must be enabled, including the information contained in the annexes (either via the Safety Monitoring System Master File itself or via access to the systems used to generate the annex content).

3.15.5. MAHs should be able to justify their approach and have document control procedures in place to govern the maintenance of the Safety Monitoring System Master File.

3.15.6. Changes to the Safety Monitoring System Master File should also account for shared Safety Monitoring Systems and delegated activities. A record of the date and nature of notifications of the changes made available to the Authority, the local QPPV and relevant third parties should be kept ensuring that change control is fully implemented.

3.15.7. The Safety Monitoring System Master File should be retained in a manner that ensures its legibility and accessibility.

3.16. Presentation

The Safety Monitoring System Master File should be continuously accessible to the local QPPV and to the Authority. The information should be concise, accurate and reflect the current system in place, which means that

whatever format is used, it must be possible to keep the information up to date and, when necessary, to revise to take account of experience gained, technical and scientific progress and amendments to the legislative requirements.

3.17. Format and layout

i. The Safety Monitoring System Master File may be in electronic form and shall be made available to the Authority upon request. In any format, the Safety Monitoring System Master File should be legible, complete, provided in a manner that ensures all documentation is accessible and allows full traceability of changes.

ii. Access to the Safety Monitoring System Master File shall be restricted to ensure appropriate control over the content and to assign specific responsibilities for the management of Safety Monitoring System Master File in terms of change control and archiving.

iii. The Safety Monitoring System Master File should be indexed in a manner consistent to allow easy navigation to the contents. In general, embedded documents are discouraged. The use of electronic book-marking and searchable text is recommended. Documents such as copies of signed statements or agreements should be included as appendices and described in the index.

iv. The documents and particulars of the Safety Monitoring System Master File should be presented with the following headings and, if in hardcopy, in the order outlined:

a) Cover Page to include:

(i) The name of the MAH, and the local QPPV responsible for the Safety Monitoring System described, as well as the relevant local QPPV and third-party company name (if applicable).

(ii) The name of other concerned MAH(s) (sharing the Safety Monitoring System), if applicable.

(iii) The list of Safety Monitoring System Master Files for the MAH (concerning products with a different Safety Monitoring System).

(iv) The date of preparation/last update.

b) The headings referred to in sections 3.5 to 3.13 should be used for the main content of the Safety Monitoring System Master File. The minimum required content of the annexes is outlined in section 3.14 and additional information may be included in the annexes, provided that the requirements for the content of the main sections are also met. The positioning of content in the Annexes is further outlined; the bullet points are descriptions of possible content (and not required headings):

(i) The Qualified Person responsible for pharmacovigilance, Annex A

(ii) The list of tasks that have been delegated by the local QPPV, or the applicable procedural document

(iii) The curriculum vitae of the local QPPV and associated documents

(iv) Contact details

(v) The Organisational Structure of the MAH, Annex B

(vi) The lists of contracts and agreements

(vii) Sources of safety data, Annex C

(viii) Lists associated with the description of sources of safety data e.g. affiliates and third-party contacts

(ix) Computerised systems and Databases, Annex D

(x) Safety monitoring Process, and written procedures, Annex E

(xi) Lists of procedural documents

(xii) Safety Monitoring System Performance, Annex F

(xiii) Lists of performance indicators

(xiv) Current results of performance assessment in relation to the indicators e.g. Quality management system, Annex G

(xv) Audit schedules

(xvi) List of audits conducted and completed Products, Annex H

(xvii) List(s) of products covered by the Safety Monitoring System

(xviii) Any notes concerning the MAH per product

(xix) Document and Record Control, Annex I

(xx) Amendment Log

(xxi) Documentation of history of changes for Annex contents, indexed according to the Annexes A-H and their content if not provided within the relevant annex itself

(xxii) Documentation to support notifications and Signatures concerning the Safety Monitoring System Master File, as required. Where there is no content for an Annex, there is no need to provide blank content pages with headings however, the Annexes that are provided should still be named according to the format described. For example, Annex E should not be renamed to Annex D in circumstances where no Annex concerning computerised systems and databases are used, Annex D should simply be described as 'unused' in the indexing, in order that recipients of the Safety Monitoring System Master File are assured that missing content is intended.

4. RISK MANAGEMENT SYSTEM

4.1. It is recognised that at the time of authorisation, information on the safety of a medicine or allied substance may be limited. This is due to many factors including the relatively small numbers of subjects in clinical trials compared with the intended treatment population, restricted population in terms of age, gender and ethnicity, restricted co- morbidity, restricted co-medication, restricted conditions of use, relatively short duration of exposure and follow up, and the statistical problems associated with looking at multiple outcomes.

4.2. A medicine or allied substance is authorised on the basis that in the specified indication(s), at the time of authorisation, the benefit-risk ratio is judged to be positive for the target population. A typical medicine or allied substance will have multiple risks associated with it and individual risks will vary in terms of severity, effect on individual patients and public health impact. However, not all actual or potential risks will have been identified at the time when authorisation is sought and many of the risks associated with the use of a medicine or allied

substance will only be discovered and characterised post authorisation.

4.3. Planning of the necessary safety monitoring activities to characterise the safety profile of the medicine or allied substance will be improved if it is more closely based on specific issues identified from pre- or post-authorisation data and from pharmacological principles.

4.4. However, the purpose of risk identification and characterisation is to allow for risk minimisation or mitigation wherever possible. Therefore, risk management has three stages which are inter-related and reiterative:

i. Characterisation of the safety profile of the medicine or allied substance, including what is known and not known;

ii. Planning safety monitoring activities to characterise risks and identify new risks and increase the knowledge in general about the safety profile of the medicine or allied substance;

iii. Planning and implementation of risk minimisation and mitigation, and assessment of the effectiveness of these activities.

iv. The overall aim of risk management is to ensure that the benefits of a particular medicine or allied

substance (or a series of medicines and allied substances) exceed the risks by the greatest achievable margin for the individual patient and for the target population.

4.5. MAH responsibility for risk management

i. In relation to risk management of its medicines and allied substances, MAH is responsible for:

   a) Ensuring that it constantly monitors the risks of its medicines and allied substances and reports the results of this, as required, to the Authority;

   b) Taking all appropriate actions to minimise the risks of the medicine or allied substance and maximise the benefits, including ensuring the accuracy of all information produced by the MAH in relation to its medicines and allied substances, and actively updating and promptly communicating it when new information becomes available.

ii. Producing an RMP requires the input of different specialists and departments within and/or outside an organisation. The safety specification may require

involvement of toxicologists, clinical pharmacologists, clinical research physicians, pharmacoepidemiologists, pharmacogenomics experts, safety monitoring experts and any other relevant expertise.

iii. The input required for the safety monitoring plan may require any of these experts depending upon the safety concerns identified in the safety specification and the types of activities planned to address them. The design of risk minimisation activities should involve people with expertise in communication and, where appropriate, patients and/or healthcare professionals. Since a risk management plan is primarily a safety monitoring document, ideally the production of it should be managed by personnel with appropriate safety monitoring training.

iv. Regardless of who prepares the RMP, the responsibility for the content and accuracy of the RMP remains with the Marketing Authorisation Holder who should ensure oversight by someone with the appropriate scientific background within the organisation.

4.6. Objective of the Risk Management Plan

ii. The RMP must contain elements which:

a) Identify or characterise the safety profile of the medicine or allied substance(s) concerned;

b) Indicate how to characterise further the safety profile of the medicine or allied substance(s) concerned;

c) Document measures to prevent or minimise the risks associated with the medicine or allied substance including an assessment of the effectiveness of those interventions;

d) Document post-authorisation obligations that have been imposed as a condition of the marketing authorisation.

iii. Additionally, an implicit requirement to fulfil these obligations in RMP should include:

a) A description of what is known and not known about the safety profile of the concerned medicine or allied substance(s);

b) Indication of 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 documents the need for studies on efficacy in the post-authorisation phase (also known as effectiveness studies);

c) A description of how the effectiveness of risk minimisation measures will be assessed.

iv. The RMP is a dynamic, stand-alone document which should be updated throughout the life cycle of the medicines and allied substances.

4.7. Structure of the Risk Management Plan

The RMP consists of seven parts:

(i) Product(s) overview

(ii) Safety specification

(iii) Safety monitoring plan

(iv) Plans for post-authorisation efficacy studies

(v) Risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures)

(vi) Summary of the risk management plan

(vii) Annexes

1. PART I PRODUCT OVERVIEW

This should provide administrative information on the RMP, and an overview of the products(s) covered within it. The information should include:

i. Active substance information:
   a) Aci. active substance(s);
   b) Pharmacotherapeutic group(s) (ATC code);
   c) Name of MAH;
   d) Date and country of first authorisation worldwide (if applicable);
   e) Date and country of first launch worldwide (if applicable);
   f) Number of medicine or allied substance(s) to which this RMP refers.

ii. Administrative information on the RMP:
   a) Data lock point of the current RMP;
   b) Date submitted and the version number;
   c) List of all Sections of the RMP with date and version of the RMP when the Section was last (updated and) submitted.

iii. For each medicine or allied substance included in the RMP:
   a) Marketing Authorisation number;
   b) Trademark/brand name(s);

c) Brief description of the product including:

d) Chemical class;

e) Summary of mode of action;

f) Important information about its composition (e.g. origin of active substance of biologicals, relevant adjuvants or residues for vaccines);

g) Indications:
   - Current (if applicable);
   - Proposed (if applicable);

h) Dosage:
   - Current (if applicable);
   - Proposed (if applicable);

i) Pharmaceutical forms and strengths:
   - Current (if applicable);
   - Proposed (if applicable);

j) Whether the product is the subject of additional monitoring.

2. PART II SAFETY SPECIFICATION

The purpose of the safety specification is to provide a synopsis of the safety profile of the medicine or allied substance(s) and should include what is known and not known about the medicine or allied substance(s). It should be a summary of the important identified risks of a medicine or allied substance,

important potential risks, and missing information. Missing information is defined as: gaps in knowledge about a medicine or allied substance, related to safety or use patient populations, which could be clinically significant (see RMP Annex I). It should also address the populations potentially at risk (where the product is likely to be used i.e. both labelled and off-labelled use), and outstanding safety questions which warrant further investigation to refine understanding of the benefit-risk balance during the post-authorisation period. In the RMP, the safety specification will form the basis of the safety monitoring plan, and the risk minimisation plan.

The safety specification consists of eight elements:

i. Epidemiology of the indication(s) and target population(s)
ii. Non-clinical part of the safety specification
iii. Clinical trial exposure
iv. Populations not studied in clinical trials
v. Post-authorisation experience
vi. Additional requirements for safety specification by the Authority
vii. Identified and potential risks
viii. Summary of the safety concerns

It is recommended that MAHs follow the structure of elements provided below when compiling the safety specification. The

elements of the safety specification that are included are only a guide. The safety specification can include additional elements, depending on the nature of the product and its development programme. Elements which might need to be incorporated include:

a. Quality aspects if relevant in relation to the safety and efficacy of the product;
b. The disposal of the product which might pose a particular risk because of remaining active substance (e.g. patches);
c. Innovative pharmaceutical forms; or
d. Use a medical device.

i. Epidemiology of the indications and target population

a. The epidemiology of the indication(s) should be discussed. This discussion should include incidence, prevalence, mortality and relevant co-morbidity, and should whenever possible be stratified by age, sex, and racial and/or ethnic origin. Differences in the epidemiology in the different regions should be discussed, where feasible, (because the epidemiology of the indication(s) may vary across regions), but the emphasis should be on the epidemiology in Zambia of the proposed indication.

b. Information should be provided on the important co-morbidities in the target population. For example: if a medicine or allied substance is intended for treating prostate cancer, the target population is likely to be men over the age of 50 years. Men over the age of 50 are also at risk of myocardial infarction. To identify whether a medicine or allied substance might be increasing the risk of myocardial infarction, it is important to know how many cases would be expected amongst prostate cancer patients (ideally) or men in the same age group, not taking the medicine or allied substance. Estimation of the risk in the target population, as compared with the same age/sex group in the general population may be particularly important if the disease itself increases the risk of a particular adverse event.

c. The RMP should include a statement of the intended purpose and impact of the product e.g. whether it is intended to prevent disease, to prevent serious outcomes due to a condition or to reduce progression of chronic disease.

ii. Non-clinical part of the safety specification

a. This should present a summary of the important non-clinical safety findings, for example:

(i) Toxicity (key issues identified from e.g. repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity);

(ii) General pharmacology (e.g. cardiovascular, including QT

interval prolongation, nervous system);

(iii) Drug interactions;

(iv) Other toxicity-related information or data.

b. What constitutes an important safety finding will depend upon the medicine or allied substance, the target population and experience with other similar compounds or therapies in the same class. Normally significant areas of toxicity (by target organ system), and the relevance of the findings to the use in humans, should be discussed. Also, quality aspects if relevant to safety (e.g. important information on the active substance or its impurities, e.g. genotoxic impurities) should be discussed. If a product is intended for use in women of childbearing age, data on the reproductive/developmental toxicity should be explicitly mentioned and the implications for use in this population discussed. Where the non- clinical safety finding could constitute an important risk to the target population, it should be included as a safety concern.

For other special populations depending upon the indication and target population, consideration should be given to whether specific non-clinical data needs exist.

iii. Clinical trial exposure

a. To assess the limitations of the human safety database, data on the patients studied in clinical trials should be provided. This data should be provided in the most appropriate format, e.g. tables/graphs. The size of the study population should be detailed using both numbers of patients and, where appropriate, patient time (patient- years, patient-months) exposed to the medicine or allied substance.

b. This should be stratified for relevant categories and by the type of trial (randomised blinded trial population only and all clinical trial populations.) Stratifications would normally include:

(i) Age and gender;
(ii) Indication;
(iii) Dose;
(iv) Racial origin.

c. Duration of exposure should be provided either graphically by plotting numbers of patients against time or in tabular format. The exposure of special populations (pregnant women, breast-feeding women, renal impairment, hepatic impairment, cardiac impairment, sub-populations with relevant genetic polymorphisms, immuno-compromised) should be provided as appropriate. The degree of renal, hepatic or cardiac impairment should be specified as well as the genetic polymorphism.

d. The categories above are only suggestions and tables/graphs should be tailored to the product. For example, indication may not be a relevant stratification for a medicine or allied substance where only one indication has been studied, and route of administration, number of courses/immunisations or repeat administrations may be important categories to be added.

e. When presenting age data, categories should be chosen which are relevant to the target population. Broad artificial divisions which are not clinically relevant, such as <65 and >65, should be avoided. Paediatric data should be divided by categories; similarly, the data on elderly patients should be considered for stratification into categories such as

65-74, 75-84 and 85+, although the age strata should reflect that of the target population. For teratogenic drugs, stratification into age categories relating to childbearing potential might be appropriate for the female population.

f. Unless clearly relevant, data should not be presented by individual trial but should be pooled. Totals should be provided for each table/graph as appropriate. Where patients have been enrolled in more than one trial (e.g. open label extension study following a trial) they should only be included once in the age/sex/ethnic origin tables. Where differences in the total numbers of patients arise between tables, the tables should be annotated to reflect the reasons for discrepancy.

g. When the RMP is being submitted with an application for a new indication, a new pharmaceutical form or route, the clinical trial data specific to the application should be presented separately at the start of the Section as well as being included in the summary tables (as described above) representing pooled data across all indications.

iv. Populations not studied in clinical trials

a. Limitations of the clinical trials should also be presented in terms of the relevance of inclusion and exclusion criteria in relation to the target population. This is particularly important when exclusion criteria are not proposed as contraindications for the drug. Lists of inclusion/exclusion criteria should not be provided by trial, but a summary of the effect of these on the overall development programme in relation to the target population should be provided.

b. The implications, with respect to predicting the safety of the product in the marketplace, for any of these populations with limited or no research should be explicitly discussed. In addition, the limitations of the database regarding the detection of adverse reactions are due to:

(i) Number of patients studied;

(ii) Cumulative exposure (e.g. specific organ toxicity);

(iii) Long-term use (e.g. malignancy) should be discussed.

c. Where the missing information could constitute an important risk to the target population, it should be included as a safety concern in RMP.

d. Populations to be considered for discussion should include (but might not be limited to):

(i) Paediatric population: children (from birth to 18 years with consideration given to the different age categories or, if justified, to other developmentally meaningful groups i.e. considering specific organ maturation). If paediatric development has been limited to certain age categories, then the implications for other paediatric age groups should also be discussed.

(ii) Elderly population: implications for use in patients over the age of 65 should be discussed – with appropriate consideration given to use in the older end of the age spectrum. The effects of impairments, e.g. renal, hepatic, or of concomitant disease or medication will be discussed mainly in the appropriate sections below, but discussion in this section should reflect the fact that in the elderly population many of these factors may co-exist. The

cumulative effects of multiple impairments and multiple medications should be discussed. Consideration of whether laboratory screening should be performed routinely before use of the medicine or allied substance(s) in the elderly should be discussed. Any adverse reactions which might be of special concern in the elderly, e.g. dizziness or central nervous system effects should be explored.

(iii) Pregnant or breast-feeding women: If the target population includes women of child-bearing age, the implications for pregnancy and/or breast-feeding should be discussed. If the medicine or allied substance is not specifically for use during pregnancy, any pregnancies which have occurred during the developmental programme and their outcomes should be discussed. For products where pregnancy should be avoided for safety reasons, the discussion on pregnancy should also include an analysis of the reasons why the contraceptive measures in place during the clinical trials failed and the implications for use in the less controlled conditions of everyday medicinal practice.

(iv) Patients with hepatic impairment

(v) Patients with renal impairment

(vi) Patients with other relevant co-morbidity (e.g. cardiovascular or immuno-compromised including organ transplant patients)

(vii) Patients with disease severity different from that studied in clinical trials

(viii) Any experience of use in patients with different disease severities should be discussed, particularly if the proposed indication is restricted to those patients with a specific disease severity.

(ix) Sub-populations carrying known and relevant genetic polymorphism: the extent of pharmacogenetic effects and the implications on genetic biomarker use in the target population should be discussed. Where a proposed drug indication constitutes patients with or without specific genetic markers, or the clinical development programme has been in patients with a specific mutation, the MAH should discuss the implications of this for the target population and explore whether use in patients with an unknown or different genotype could constitute a safety concern. If a potentially

clinically important genetic polymorphism has been identified but not fully studied in the clinical development programme, this should be considered as missing information and/or a potential risk. This should be reflected in the safety specification and safety monitoring plan. Whether it is included as a safety concern for the purposes of risk minimisation will depend upon the importance of the possible clinical implications.

(x) Patients of different racial and/or ethnic origins: information on racial origin may be relevant and valuable for evaluation of efficacy and safety and for preventing adverse reactions or improving benefits in the target population. The experience of drug use in patients with different racial and/or ethnic origins should be discussed including the implications on efficacy and safety, based on pharmacokinetics and pharmacodynamics, in the target population. If it is likely that efficacy or safety may be affected by race or ethnicity, consideration should be given to including this either as a safety concern or as a topic for inclusion in RMP. Consideration should also be given as to

whether post- authorisation efficacy and/or safety studies are necessary.

v. Post-Authorisation Experience

The purpose is to provide information on the number of patients exposed post authorisation; how the medicine or allied substance has been used in practice and labelled and off-label use including use in the special populations mentioned in RMP. It should also include brief information on the number of patients included in completed observational studies conducted either to elucidate a safety issue or for drug utilisation purposes. Details of significant actions taken to update information on the safety of the medicine or allied substance should also be provided.

a. **Action taken by regulatory authorities and/or MAHs for safety reasons**

(i) List any significant regulatory action (including those initiated by the MAH), in any market, taken in relation to a safety concern. Significant regulatory action would include: a restriction to the approved indication, a new contra-indication, a new or strengthened warning or any action to suspend or revoke a Marketing Authorisation. The Authority will perform oversight monitoring of the

implementation of MAH risk minimization activities.

(ii) This list should be cumulative, and specify the country, action taken and the date as appropriate. Rollout in multiple countries of a new safety statement initiated by the MAH can be presented as one action.

(iii) When the RMP is updated, a brief description of the reasons leading to any significant actions since the last submission of the RMP should be provided to the Authority. It may be appropriate to add comments if the regulatory action taken is not applicable to certain products/formulations.

b. **Non-study post-authorisation exposure**

(i) Where marketing of the medicine or allied substance has occurred, the MAH should provide cumulative data on patients exposed post-marketing. Where possible, the information should be stratified by relevant variables. These may include age, sex, indication, dose and region. Depending upon the medicine or allied substance, other variables may be relevant such as number of vaccination

courses, route of administration or duration of treatment.

(ii) When deciding which measure to use for exposure data, it is important to consider the way a medicine or allied substance is used. Exposure data based on the number of kilo grammes of medicine or allied substance sold divided by the average dose is only valid if the medicine or allied substance is always used at one dose level for a fixed length of time, which is not the situation with most medicines and allied substances. In paediatric populations or mixed populations of different indications or age groups, use of this measure alone is inappropriate, and other measures should be used. For example, for medicines and allied substances used chronically, the appropriate measure may be patient years of use. However, when use is typically limited and utilisation is determined by pack size (e.g. a course of antibiotics), a simple count of packs sold may be more appropriate.

(iii) If the drug has different routes of administration, e.g. subcutaneous or oral, exposure data should be presented separately, where possible. The

Authority may request additional stratification of exposure data, e.g. exposure in age groups or within different approved indications. However, if the drug is used in different indications with different dosing schedules or other delineating factors suitable for stratification, MAHs should consider routinely providing such data where possible.

(iv) A more accurate breakdown of drug exposure based on market research should be provided where possible.

(v) If a drug utilisation study has been performed, for reimbursement or other reasons, the results, as they reflect use in the real-world setting, should be provided.

c. **Post-authorisation uses in populations not studied in clinical trials**

(i) Where there are data on post-authorisation use in the special populations identified in RMP as having no or limited exposure, estimation of the numbers exposed, and the method of calculation should be provided whether the usage is on- or off-label.

(ii) Information on the safety profile of the medicine or allied substance in these special

populations, as compared with the rest of the target population, should also be provided. Any information regarding an increased or decreased benefit in a special population should be provided. Any special population found to be at an increased or decreased risk in relation to a particular safety concern should be discussed under the specific risk in RMP, but reference should be made to this section as to which risks and populations are affected.

d. **Post-authorisation off-label use**

Post marketing updates to the safety specification should include information on off-label use. Off-label use includes use in non-authorised paediatric age categories. Information from drug utilisation studies (or other observational studies where indication is a variable) should be provided where available. When off-label use is a safety concern or a concern has been raised regarding off-label use, MAHs should attempt to quantify such use along with a description of the methods used to arrive at these figures.

e. **Epidemiological study exposure**

MAHs should provide a listing of epidemiological studies which are, or have been, conducted to elucidate

safety or efficacy issues, study drug utilisation or measure effectiveness of risk minimisation measures. This listing should include studies undertaken by the MAH itself or funded by them via a grant, whether specific or unconditional. Studies undertaken by a marketing partner, or where the MAH has been sent the results by a third party, should also be included. Information on the study title, study type (e.g. cohort, case control), population studied (including country and other relevant population descriptors), duration of study, number of persons in each category (e.g. cases, controls, exposure), disease as appropriate, person time (if appropriate) and study status (completed or on-going) should be provided. If a study has been published, a reference should be included in this RMP section, a synopsis should be included in RMP annex 5 and the publication provided in RMP annex 12.

vi. Additional Requirements for the Safety Specification

a. Potential for harm from overdose

Special attention should be given to medicines and allied substances where there is an increased risk of harm from overdose, whether intentional or accidental. Examples include medicines and allied substances where there is a narrow therapeutic margin or potential for major dose-related toxicity,

and/or where there is a high risk of intentional overdose in the treated population (e.g. in depression). Where harm from overdose has occurred during clinical trials this should be explicitly mentioned. The potential for harm from overdose should be discussed in this section and, where appropriate, overdose should be included as a safety concern in RMP and appropriate risk minimisation proposed in RMP.

b. **Potential for transmission of infectious agents**

The MAH should discuss the potential for the transmission of an infectious agent. This may be because of the nature of the manufacturing process or the materials involved. For vaccines, any potential for transmission of live virus should be discussed.

c. **Potential for misuse for illegal purposes**

The potential for misuse for illegal purposes should be considered. Misuse refers to situations where the medicine or allied substance is intentionally and inappropriately used not in accordance with the authorised product information. Misuse for illegal purposes has the additional connotation of an intention of misusing the medicine or allied substance to cause an effect in another person.

This includes, amongst others: the sale, to other people, of medicines for recreational purposes and use of a medicine or allied substance to facilitate assault. If appropriate, the means

of limiting this, e.g. using colorants and/or flavourings in the dosage form, limited pack size and controlled distribution should be discussed in the risk minimisation plan.

d. **Potential for medication errors**

a) For the purposes of the RMP, medication error refers to any unintended error in the prescribing, dispensing or administration of a medicine or allied substance while in the control of the healthcare professional, patient or consumer. Medication errors are an important cause of morbidity and mortality, and many could be prevented or mitigated. They fall broadly into 4 categories:

(i) Wrong medication;

(ii) Wrong dose (including strength, form, concentration, amount);

(iii) Wrong route of administration;

(iv) Wrong patient

b) MAHs should consider routinely the likelihood of medication errors. They should assess, prior to marketing, common sources of medication errors.

c) If a product has potential for serious harm when administered by an incorrect route, consideration should be given as to how such administration can be avoided. This is particularly important when it is common practice to administer the product at the same

time as other medicines and allied substances given by the hazardous route. In this situation, medication errors should be included as a safety concern.

d) The need for visual (or physical) differentiation between strengths of the same medicine or allied substance and between other medicines and allied substances commonly administered or taken at the same time should be discussed. In addition, if there are other products containing the same active substance on the market with formulations which are not proven to be bioequivalent, measures to avoid medication error should be discussed and appropriate risk minimisation activities proposed.

e) When a medicine or allied substance is likely to be used by a visually impaired population, special consideration should be given to the potential for medication error. Where appropriate, medication error should be included as a safety concern and appropriate risk minimisation measures proposed to address the possibility of medication error due to visual impairment.

f) Consideration should be given to the prevention of accidental ingestion or other unintended use by children.

g) Medication errors identified during product development including clinical trials should be

discussed and information on the errors, their potential cause(s) and possible remedies given. Where applicable an indication should be given of how these have been considered in the final product design.

h) If during the post-marketing period it becomes apparent that adverse reactions are occurring because of medication errors, this topic should be discussed in the updated RMP and ways of limiting the errors proposed.

i) If the formulation or strength of a product is being changed, where appropriate, medication error should be included as a safety concern and the measures that the MAH will put in place to reduce confusion between old and new "product" should be discussed in the risk minimisation plan. Similarly, it may be appropriate to discuss risk minimisation activities in relation to changes to the presentation, pack size, route of administration or release characteristics of the medicine or allied substance.

j) If the product is to be administered with a medicinal device (integrated or not), consideration should be given to any safety concerns which could represent a risk to the patient (medicinal device malfunction).

e. **Potential for off-label use**

a) The potential for off-label use should be discussed. Off-label use relates to situations where the medicine or allied substance is intentionally used for a medicinal purpose not in accordance with the authorised product information. This is particularly relevant where a medicine or allied substance has an indication restricted to a subset of the population within a disease area or there are situations where the medicine or allied substance must not be given for safety reasons. The potential for use in other disease area should also be considered where this is likely.

b) Where appropriate, use could be made of data on actual use versus authorised use in other markets.

f. **Specific paediatric issues**

This section deals with aspects of paediatric use not covered under "Populations not studied".

g. **Issues identified in paediatric investigation plans**

a) Any recommendations for long-term follow up of safety or efficacy issues in relation to paediatric use which are mentioned in the paediatric investigation plan should be detailed here. This section should clarify if, and how, this had been considered in "Additional

Requirements for the Safety Specifications ix to xiii. If the issue has been resolved following further development, or is no longer considered of sufficient impact to justify listing as a safety concern, this should be discussed and justified.

b) Proposals for specific long-term paediatric studies should be considered at the time of application for a paediatric indication and if felt not to be necessary justification should be provided. If an indication in adults precedes an application for paediatric use, any registries established to provide data on use of the product in real medicinal practice should avoid age related exclusion criteria so that any potential off-label use in the paediatric population can be included.

c) In some circumstances, the safety concern identified in the paediatric investigation plan may be applicable to the whole population being treated. In these cases, consideration should be given as to whether some of the safety monitoring activities and/or risk minimisation activities from the paediatric investigation plan are appropriate for, and should be extended to, the whole population. For these safety concerns, this RMP section should also include details of how the specific paediatric aspects will be addressed and all paediatric investigation plan recommendations considered.

d) Cross-reference may be made to "populations not studied in clinical trials" and "identified and potential risks".

h. **Potential for paediatric off-label use**

If the disease or disorder which is being treated or prevented is found in the paediatric population, and the product is not authorised in all paediatric age groups, the potential for off-label paediatric use in the non- authorised age groups should be discussed. If there are limited treatment options, it should not be assumed that clinicians will adhere to the labelled indication, so it is important that potential paediatric issues are discussed. Any actual use should be discussed in "Non-study post-authorisation exposure" and in "Post-authorisation uses in populations not studied in clinical trials".

vii. Identified and Potential Risks

This provides information on the important identified and potential risks associated with use of the product. These should include only the important identified and potential adverse events/reactions, important identified and potential interactions with other medicines and allied substances, foods and other substances, and the important pharmacological class effects.

a. **Newly identified safety concerns**

Safety concerns (important identified and important potential risks) identified since the last submission of the RMP should be listed here and further discussed in the appropriate section below. The source of safety concern should be stated whether it is an important identified or important potential and whether new studies or risk minimisation activities are proposed (with further details in the appropriate RMP parts).

b. **Recent study reports with implications for safety concerns**

Study reports (either interim or final, from whichever type of study), since the last RMP, which contain results which have a significant impact on an existing safety concern should be discussed here. The conclusions should be incorporated into the other sections of the safety specification as appropriate.

c. **Details of important identified and potential risks from clinical development and post-authorisation experience**

This RMP section should be concise and provide more information on the important identified and potential risks. What constitutes an important risk will depend upon several factors including the impact on the individual patient, the seriousness of the risk and the impact on public health. Normally, any risk which is clinically important and which is/is

likely to be included in the contraindications or warnings and precautions section of the summary of product characteristics (SmPC) should be included here.

d. **Identified and potential interactions including food-drug and drug- drug interactions**

Pharmacological class effects Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed in relation to both the treatments for the condition, but also in relation to commonly used medications in the target population. For each, the evidence supporting the interaction and possible mechanism should be summarised, and the potential health risks posed for the different indications and in the different populations should be discussed. Interactions which are important clinically should be included as a safety concern in "Summary of the safety concerns."

e. **Identified and potential risks (ATMP version)**

a) Advanced therapy medicines and allied substances (ATMPs) because of their nature may have specific risks that are usually not applicable to other non-advanced therapy medicines and allied substances.
b) Newly identified safety concerns (ATMP)
c) Recent study reports with implications for safety concerns (ATMP)

d) Details of important identified and potential risks (ATMP)

viii. Summary of the Safety Concerns

a) At the end of the RMP part "Safety specification" a summary should be provided of the safety concerns.

b) A safety concern is:

(i) An important, identified risk;
(ii) An important potential risk; or
(iii) Missing information (see Annex I).

c) For RMPs covering multiple products where there may be significant differences in the important identified and important potential risks for different products, it may be appropriate to subdivide the summary of safety concerns under specific headings with the relevant identified and potential risks under each heading. Headings which could be considered include:

(i) Safety concerns relating to the active substance;
(ii) Safety concerns related to a specific formulation or route of administration;
(iii) Safety concerns relating to the target population;
(iv) Risks associated with switching to non-prescription status.

d) Division of safety concerns by headings should only be considered when the risks clearly do not apply to some products and inclusion as a single list could cause confusion.

3. PART III SAFETY MONITORING PLAN

The purpose of the safety monitoring plan is to discuss how the MAH plans to identify and/or characterise the risks identified in the safety specification.

i. It provides a structured plan for:

   a) The identification of new safety concerns;
   b) Further characterisation of known safety concerns including elucidation of risk factors, increased frequency of safety concern, change in pattern of a known safety concern;
   c) The investigation of whether a potential safety concern is real or not;
   d) How missing information will be sought.
   e) It does **NOT** include actions intended to reduce, prevent or mitigate risks.

ii. The safety monitoring plan should be based on the safety concerns summarised "summary of the safety concerns" of the safety specification. Early discussions between the

Authority and the MAH are recommended to identify whether, and which, additional safety monitoring activities are needed. It is important to note that only a proportion of risks are likely to be foreseeable and therefore signal detection, which is part of routine safety monitoring, will be an important element in identifying new risks for all products.

iii. Safety monitoring activities can be divided into routine safety monitoring activities and additional safety monitoring activities. For each safety concern, the MAH should list their planned safety monitoring activities for that concern. Safety monitoring plans should be proportionate to the risks of the product. If routine safety monitoring is considered sufficient for post- authorisation safety monitoring, without the need for additional actions (e.g. safety studies) "routine pharmacovigilance" should be entered against the safety concern.

a. Routine safety monitoring activities

i. Routine safety monitoring is the set of activities required to fulfil the legal requirements for Safety Monitoring Regulations. The Safety Monitoring System Master File contains details of the system and processes each MAH has in place to achieve this.

ii. In certain situations, the Authority may make recommendations for specific activities related to the

collection, collation, assessment and reporting of spontaneous reports of adverse reactions which differ from the normal requirements for routine safety monitoring.

b. Specific adverse reaction follow-up questionnaires

i. Where MAH is requested, or plans to use, specific questionnaires to obtain structured information on reported adverse reactions of special interest, copies of these forms should be provided in RMP annex 7 and will be made available upon request. MAHs are encouraged to use the same or similar questionnaires for the same adverse event to decrease the burden on healthcare professionals.

ii. Use of specific questionnaires as a follow-up to a reported suspected adverse reaction is routine safety monitoring.

c. Additional safety monitoring activities

i. Additional safety monitoring activities may be non-clinical studies, clinical trials or non- interventional studies. A safety concern may have no, or several additional safety monitoring activities associated with it depend upon its nature, the degree to which it has already been characterised, and the feasibility of

studying it. MAHs should consider the situations when additional safety monitoring activities are needed. For example, a medicine or allied substance intended for chronic use may only have relatively short term follow up data at the time of authorisation. Long term follow-up of patients from the clinical trial population or a cohort study may provide additional reassurance on the long-term effects of the medicine or allied substance. A medicine or allied substance, where there is conflicting pre-clinical data, e.g. carcinogenicity in only one species, may also require long-term follow-up of a cohort of patients to confirm that there is not an increased risk of cancer in human use. Another example, when additional safety monitoring activities should be considered, is when a potential risk with an individual medicine or allied substance has a significant background incidence in the target population(s), leading to difficulties in distinguishing between the effects of the medicine or allied substance and the "normal" incidence. If any doubt exists about the need for additional safety monitoring activities, consultation with the Authority should be considered.

ii. The objective(s) of additional safety monitoring activities will normally differ according to the safety concern to be addressed. For important identified and

potential risks, objectives may be to measure the incidence rate in a larger or a different population, to measure the rate ratio or rate difference in comparison to a reference medicine or allied substance, to examine how the risk varies with different doses and durations of exposure, to identify risk factors or to assess a causal association. For missing information, the objective may simply be to investigate the possibility of a risk or to provide reassurance about the absence of a risk.

iii. Studies in the safety monitoring plan should relate to the safety concerns identified in the safety specification whether the studies are to identify and characterise risks, or to assess the effectiveness of risk minimisation activities. The MAH should include all studies designed to address safety concerns or measure the effectiveness of risk minimisation measures. This includes all post-authorisation safety studies which are initiated, managed or financed by MAHs, voluntarily, or pursuant to obligations imposed by the Authority.

iv. Pharmacoepidemiology studies included in the safety monitoring plan should be designed and conducted with expert advice and in accordance with good pharmacoepidemiology practices. The responsibility for the scientific value of study protocols remains with

MAHs, even if they have been previously discussed with the Authority.

v. For some safety concerns, additional safety monitoring activities other than pharmacoepidemiology studies may be required, e.g. pharmacokinetic studies, clinical trials or further pre-clinical work.

d. Situations with post authorisation safety studies

This section should be read in conjunction with Section 8 on post-authorisation safety studies.

e. Studies to measure the effectiveness of risk minimisation measures

Post-authorisation safety studies (PASS) include in their definition studies which measure the effectiveness of risk management measures. Studies looking at the effectiveness of risk minimisation measures should be included in the safety monitoring plan against the specific safety concern(s) as well as described in detail in the risk minimisation plan.

f. Drug utilisation studies

Drug utilisation studies may be requested by the Authority to monitor drug usage in the country. Although they may not be initiated to collect safety data, they can provide useful

information on whether risk minimisation activities are effective and on the demographics of target populations.

g. Registries

A registry is an organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition, or exposure. A registry can be used as a data source within which studies can be performed. Entry in a registry is generally defined either by diagnosis of a disease (disease registry) or prescription of a drug (exposure registry).

h. Action plans for safety concerns with additional safety monitoring requirements

i. For safety concerns with additional safety monitoring activities only, the action plan for each safety concern should be presented according to the following structure:

a) Safety concern;
b) Proposed action(s);
c) Individual objectives of proposed action(s) (i.e. what aspects of safety concern they are intended to characterise); and for each action:
d) Details of individual action;
e) Steps; and

f) Milestones (including expected dates)

h. Summary table of additional safety monitoring activities

i. The summary table of the safety monitoring plan should provide clarity to all stakeholders as to which category an activity in the safety monitoring plan falls under, i.e.:

a) Imposed obligations as a condition of the MA;
b) Specific Obligations in the framework of a MA under exceptional circumstances;
c) Required to investigate a safety concern in the RMP or to evaluate the effectiveness of risk minimisation activities;
d) Other studies conducted by MAH which may provide safety information but are not considered to be significant in investigating safety concerns or the effectiveness of risk minimisation activities.

4. PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

i. Efficacy, as assessed at the time of authorisation, is based on data from clinical trials which, by their nature, are of relatively limited duration (e.g. usually between 6 months to 3 years). The benefit (efficacy of the

medicine) risk balance must be positive for a medicine to be authorised. Whereas it is recognised that many risks will be identified post authorisation, there is an implicit assumption that efficacy remains relatively constant over time. This may not always be valid.

ii. For most medicines there will not be a need for post-authorisation efficacy studies.

iii. Paediatric medicines and allied substances and advanced therapy medicines and allied substances need long term follow-up of efficacy as part of post-authorisation surveillance.

Summary of existing efficacy data

i. As background to any proposed post-authorisation efficacy studies, and to provide context for the summary of the RMP, there should be a summary of the efficacy of the product and the studies and endpoints on which it was based. Where the RMP covers more than one medicine or allied substance, the information should be provided by medicine or allied substance to permit easy extraction for the summary of the RMP Section. Similarly, medicines and allied substances with more than one indication should have a separate summary of efficacy for each indication.

ii. The summary of efficacy (one page maximum per indication/population) should be in lay language and the following should be considered for inclusion:

a) Current (gold) standards of treatment;
b) Where the medicine or allied substance fits in the therapeutic armamentarium (i.e. 1st line, relapse, etc.);
c) A brief statement of the standard against which the medicine was judged;
d) Number of patients in pivotal studies and treatment regimens;
e) Results in lay language.

iii. The following areas should be discussed briefly and the need for further studies post authorisation evaluated:

a) The robustness of the endpoints on which the efficacy evaluation is based;
b) Applicability of the efficacy data to all patients in the target population;
c) Factors which might affect the efficacy of the product in everyday medical practice;
d) Variability in benefits of treatment for sub-populations.

iv. For updates to the RMP, any subsequent data which impacts on efficacy should be mentioned and its impact

on the benefits of the medicine or allied substance discussed.

Tables of post-authorisation efficacy studies

i. A summary table showing an overview of the planned studies together with timelines and milestones should be provided here with the (draft) protocols for these studies included in RMP annex.

ii. Efficacy studies which have specific obligations and/or conditions of the MAH should also be included in this part of the RMP.

iii. Efficacy studies which have specific obligations and/or conditions of MAH:

a) Description of study
b) Milestone (maybe several per activity)
c) Due date (maybe several per activity)
d) Other Efficacy and effectiveness studies
e) Description of study
f) Milestone (maybe several per activity)
g) Due date (maybe several per activity)

5. PART V RISK MINIMISATION MEASURES

i. Based on safety specifications, MAH should assess what risk minimisation activities are needed for each safety concern. The risk minimisation plan should

provide details of the risk minimisation measures which will be taken to reduce the risks associated with individual safety concerns. It is not possible to provide precise guidance on which risk minimisation activity should be used in a given situation as each safety concern needs to be considered on a case-by-case basis and will depend upon the severity of the risk, the healthcare setting, the indication, the pharmaceutical form and the target population. A safety concern may be addressed using more than one risk minimisation measure.

ii. For active substances where there are individual products with substantially different indications or target populations, it may be appropriate to have a risk minimisation plan specific to each product. Examples when multiple risk minimisation plans could be considered include:

a) An active substance where there are products with both prescription only and non-prescription legal status;

b) Medicines and allied substances where there are major risks, and the indications cross areas of medical expertise. In the latter case, there could be diverse educational needs for different specialists since the areas of specialised knowledge will be distinct. For example, an active substance which causes important

QT prolongation would most likely not need educational material explaining the implications of this and the interactions with other products if the product were intended solely for use by cardiologists in a hospital setting but might need educational material if intended for use in general practice or orthopaedic surgery where it is unlikely that prescribers will have this specialist knowledge;

c) Active substances where there are major risks which differ according to the target population.

iii. Risk minimisation activities may consist of routine risk minimisation (e.g. measures associated with locally authorised product labelling) or additional risk minimisation activities (e.g. Direct Healthcare Professional Communications/educational materials/controlled distribution systems). All risk minimisation measures should have a clearly identifiable objective.

iv. All risk minimisation measures should be reviewed at regular intervals and their effectiveness assessed.

Routine risk minimisation

i. Routine risk minimisation activities are those which apply to every medicine or allied substance. These relate to:

a) Summary of product characteristics;
b) The labelling;
c) The package leaflet;
d) The pack size(s);
e) The legal status of the product.

ii. The summary of product characteristics (SmPC) and the package leaflet are important tools for risk minimisation as they constitute a controlled and standardised format for informing healthcare practitioners and patients about the medicine or allied substance. The design of the packaging, and even the formulation itself, may play an important role in preventing medication error.

Pack size

i. Since every pack size is specifically authorised for a medicine or allied substance, planning the number of "dosage units" within each pack, and the range of pack sizes available can be considered a form of routine risk management activity. In theory, controlling the number

of "dosage units" should mean that patients will need to see a healthcare professional at defined intervals: increasing the opportunity for testing and reducing the length of time a patient is without review. In extreme cases, making units available in only one pack size to try to link prescribing to the need for review may be considered.

ii. A small pack size can also be useful, especially if overdose is thought to be a major risk or if the potential for drugs to get into the general population needs to be controlled.

Legal status

i. Controlling the legal status under which a medicine or allied substance may be made available can reduce the risks associated with its use or misuse. This can be achieved by controlling the conditions under which a medicine or allied substance may be prescribed, or the conditions under which a patient may receive a medicine or allied substance.

ii. When a Marketing Authorisation is granted, it must include details of any conditions or restrictions imposed on the supply or the use of the medicine or allied substance, including the conditions under which a medicine or allied substance may be made available to

patients. The conditions under which a medicine or allied substance is made available is commonly referred to as the "legal status" of a medicine or allied substance. Typically, it includes information on whether the medicine or allied substance is subject to medicinal prescription. It may also restrict where the medicine or allied substance can be administered (e.g. in a hospital but see below) or by whom it may be prescribed (e.g. specialist).

iii. For medicines and allied substances only available on prescriptions, additional conditions may be imposed by classifying medicines and allied substances into those available only upon either a restricted medical prescription or a special medical prescription.

Restricted medical prescription

This may be used to control who may initiate treatment, prescribe the medicine or allied substance and the setting in which the medicine can be given or used. When considering classification of a medicine or allied substance as subject to restricted medicinal prescription, the following factors should be considered:

a) The medicine or allied substance, because of its pharmaceutical characteristics or novelty or in the

interests of public health, is reserved for treatments which can only be followed in a hospital environment;

b) The medicine or allied substance is used for the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow-up may be carried out elsewhere; or

c) The medicine or allied substance is intended for outpatients, but its use may produce very serious adverse reactions requiring prescription drawn up as required by a specialist and special supervision throughout the treatment.

Special medical prescription

i. For classification as subject of special medical prescription, the following factors should be considered:

a) The medicine or allied substance contains, in a non-exempt quantity, a substance classified as a narcotic or a psychotropic substance within the meaning of the international conventions in force, such as the United Nations Conventions of 1961 and 1971; or

b) Medicine or allied substance is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes; or

c) The medicine or allied substance contains a substance which, because of its novelty or properties, could be considered as belonging to the group envisaged in the previous indent as a precautionary measure.

ii. Most safety concerns may be adequately addressed by routine risk minimisation activities. However, for some risks, routine risk minimisation activities will not be sufficient and additional risk minimisation activities will be necessary.

Additional risk minimisation activities

i. Additional risk minimisation activities are those risk minimisation measures which are not the routine risk minimisation activities listed above. Additional risk minimisation activities should only be suggested when essential for the safe and effective use of the medicine or allied substances and these should be science-based and developed and provided by suitably qualified people. If additional risk minimisation activities are proposed, these should be detailed and a justification of why they are needed provided.

ii. Many additional risk minimisation tools are based on communication which aims to augment the information in the summary of product characteristics (SmPC) and the package leaflet. Any communication material

should be clearly focused on the risk minimisation goals and should not be confused or combined with promotional material for marketing campaigns. MAH should discuss risk minimisation plans with the Authority as early as is feasible when it is likely that specific risk minimisation activities will need to be adapted to the health care system.

iii. Where possible and appropriate, proposed risk minimisation activities should be discussed with patients and healthcare professionals if it is likely that risk minimisation activities will be directed towards them.

Educational material

i. Any educational material should be non-promotional. It is recommended that communication experts, patients and healthcare professionals are consulted on the design and wording of educational material and that, where appropriate, it is piloted before releasing for use.

ii. The final version of the educational material will need to be approved by the Authority who will check that the material contains the key elements in an appropriate design and format and is not promotional.

iii. For public health reasons, MAHs for the same active substance may be required by the Authority to have

educational material with as similar as possible layout, content, colour and format to avoid patient confusion. This requirement may also be extended to other patient material such as patient alert cards and patient monitoring cards. For this reason, MAHs are strongly recommended to avoid the use of company logos or other trademarked or patented material in educational material.

Format of risk minimisation plan(s)

i. Each safety concern identified in the summary of the safety specification should be addressed. If no risk minimisation activity is proposed, then "none proposed" should be entered against the objective.

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

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

f) Milestones for evaluation and reporting.

iii. For routine risk minimisation activities, the proposed text in the summary of product characteristics (SmPC), or a précis, should be provided along with details of any other routine risk minimisation activities proposed for that safety concern.

Evaluation of the effectiveness of risk minimisation activities

i. The success of risk minimisation activities in delivering these objectives needs to be evaluated throughout the lifecycle of a product to ensure that the burden of adverse reactions is minimised and hence the overall benefit-risk balance is optimised.

ii. When the RMP is updated, the risk minimisation plan should include an evaluation of the impact of routine and/or additional risk minimisation activities as applicable.

iii. Results of any studies to assess the impact or other formal assessment(s) of risk minimisation activities should be included when available. As part of this critical evaluation, the MAH should make observations on factors contributing to the success or weakness of risk minimisation activities. If a particular risk minimisation strategy proves ineffective, or to be

causing an excessive or undue burden on patients or the healthcare system then alternative activities need to be put in place. The MAH should always comment on whether additional or different risk minimisation activities are needed for each safety concern.

iv. In certain cases, it may be judged that risk minimisation cannot control the risks to the extent possible to ensure a positive benefit-risk balance and that the medicine or allied substance needs to be withdrawn either from the market or restricted to those patients in whom the benefits outweigh the risks.

Gap analysis

Where the safety data for a specific product is obtained from a different region, the MAH should include a gap analysis of the safety specifications, safety monitoring plan and risk minimization activities in the risk management plan. The gap analysis should discuss the differences between RMP developed for Zambia and that of the other region, highlighting and justifying any gaps or missing information.

6. PART VI SUMMARY OF RISK MINIMISATION MEASURES

A table summarising the routine and additional risk minimisation activities by safety concern should be provided.

Summary of activities in the risk management plan by medicine or allied substance

i. A summary of the RMP for each medicine or allied substance should be made publicly available. The summary must include key elements of the RMP with a specific focus on risk minimisation activities. Regarding the safety specification of the medicine or allied substance concerned, it should contain important information on potential and identified risks as well as missing information.

ii. It is difficult for one summary to satisfy the needs of all stakeholders and there may be a need for a summary of the RMP to be provided for different stakeholders in varying formats. The summary of the RMP will be evaluated during the assessment of the RMP.

Format and content of the summary of the RMP

i. This is a scientific summary, written for the lay reader to fulfil the requirements in the regulation. In situations where the RMP covers more than one product, a

separate "summary of risk minimisation measures" and "summary of activities in the risk management plan" should be prepared for each product. To present a balanced picture, the risks discussed in the RMP should be put into context with a very concise and focused description of the benefits of the medicine or allied substance. Technical terms, scientific abbreviations or acronyms should be avoided or explained in full if deemed necessary.

ii. The summary of the "risk minimisation measures" and "summary of activities in the risk management plan" should contain the following information:

a) Overview of disease epidemiology;
b) Summary of treatment benefits;
c) Unknowns relating to treatment benefits;
d) Summary of safety concerns:
   (i) Important identified risks;
   (ii) Important potential risks;
   (iii)Missing information;
e) Summary of risk minimisation activities by safety concern;
f) Planned post authorisation development plan;
g) Studies which are a condition of the Marketing Authorisation;

h) Major Changes to the Risk Management Plan over time.

iii. The information provided in each section should be brief, focused and in accordance with the word limits in the templates.

Overview of disease epidemiology

i. The MAH should summarise the epidemiology of the disease/condition the medicine or allied substance is intended to treat or prevent in a non-alarmist manner and in language appropriate to the target population. If the product is used in a range of disease severity, this fact should be emphasised and discussed. Sensitivity should be used when presenting the morbidity and mortality of the disease whilst retaining factual accuracy.

ii. If success of treatment is measured using survival figures, appropriate emphasis should be given to the fact that, by definition, survival (e.g. 5-year survival) figures relate to historical treatment. If the product is a diagnostic product used for anaesthesia or similar usage not associated with a particular disease/condition, then this section of the overview may be omitted.

Summary of treatment benefits

This should consist of very concise high level key messages concerning the results of the pivotal trials and any important supplementary evidence and should adhere to the word limits in the template.

Unknowns relating to treatment benefits

This should discuss the applicability of efficacy to all patients in the target population. It should describe very briefly any relevant parts of the target population where experience is limited and whether efficacy is expected to be different in these people, e.g. factors such as age, sex, race.

Summary of safety concerns

i. This section should briefly describe the safety concerns in suitable language for the general public. It should include the frequency and severity of the safety concern for the important identified risks and their preventability.

Risk	**What is known**	**Preventability**
Risk 1		
Risk 2 etc		

ii. For important potential risks the reasons why, it is thought to be a Risk 2 etc. potential risk (e.g. toxicology in animal study, known effect in other members of the pharmaceutical class) should be explained together with the uncertainties, e.g. "occurs in other medicines and allied substances in the same class but was not seen in the clinical trials for this medicine or allied substance which studied 3,761 people".

Risk	**What is unknown**
Risk 1	
Risk 2 etc	

iii. For missing information, it should be stated (using the above format as well) that there is no, or insufficient information regarding safety concerns, the possible relevance to the target population should be highlighted as well as the associated recommendations, e.g. contraindication, use with caution.

Summary of risk minimisation activities by safety concern

Details of routine risk minimisation measures will be provided in the published summary by a link to the product information. For each safety concern which has additional risk minimisation measures, brief details of the measures for that concern should

be provided. The objective and rationale for each measure should be stated along with the proposed actions.

Planned post-authorisation development plan

Data should be presented in the form of a table showing the planned activities in terms of efficacy studies and the further investigation of safety concerns. This table would combine the data from "summary table of additional pharmacovigilance activities", " plans for post authorisation efficacy studies", " summary of existing efficacy data". Each row of the table should include the name of the study, objectives for the study, the safety concern or efficacy issue being addressed, the status and planned date for submission of the results.

List of studies in post authorisation development plan

Study	**Objectives**	**Safety Concern/ Efficacy issue addressed**	**Status**	**Planned date of submission of interim and final results**
Study 1				
Study 2 etc				

Studies which are a condition of Marketing Authorisation

Statement on which studies in the above table are conditions of the MA e.g. "None of the above studies is a condition of the Marketing Authorisation."

Summary of changes to the risk management plan over time

This table should provide a listing of all significant changes to the RMP in chronological order. This should include, for example, the date and version number of the RMP when new safety concerns were added or existing ones removed or changed, dates and version of the RMP when new studies were added or finished, and a brief summary of changes to risk minimisation activities and the associated dates these changes were agreed. Since changes to risk minimisation activities involve a variation, the date used for changes to risk minimisation activities should be agreed with the Authority. The date for safety concerns and studies should be the date of the RMP on which they are first added.

7. PART VII ANNEXES TO THE RISK MANAGEMENT

The RMP should contain the annexes listed below. RMP annexes 1 to 3, 10 and 11 should be provided for each medicine or allied substance within the RMP. If no information is available for the given annex this should be stated. If a single

study addresses issues in "safety monitoring plan" of the RMP, it should be included in RMP annex 6 with a cross reference in RMP annex 8.

a. RMP annex 1: Interface between RMP and National Data Base (electronic only)
b. RMP annex 2: Current (or proposed if product is not authorised) summary of product characteristics (SmPC) and package leaflet.
c. RMP annex 3: Worldwide Marketing Authorisation status by country. This should include:
   (i) Current licence status (approved/refused/ under review/ suspended/expired/withdrawn);
   (ii) Date(s) of approval/refusal/suspension/expiration/withdrawal ;
   (iii) Date(s) marketed/withdrawn from market;
   (iv) Trade name(s);
   (v) Any explanatory comments.
d. RMP annex 4: Synopsis of on-going and completed clinical trial programme.
e. RMP annex 5: Synopsis of on-going and completed pharmacoepidemiological study programme.
f. RMP annex 6: Protocols for proposed and on-going studies in categories 1-3 of the section

g. "Summary table of additional pharmacovigilance activities".
h. RMP annex 7: Specific adverse event follow-up forms.
i. RMP annex 8: Protocols for proposed and on-going studies.
j. RMP annex 9: Synopsis of newly available study reports
k. RMP annex 10: Details of proposed additional risk minimisation activities (if applicable).
l. RMP annex 11: Mockup examples in English of the material provided to healthcare professionals and patients
m. RMP annex 12: Other supporting data (including reference material).

Zambia Specific Annex to the Global or EU-RMP

The Authority requires that, where an existing global or EU RMP is submitted, a Zambia Specific Annex is included to the Global or EU RMP.

The Zambia Specific Annex should identify any differences between the Global or EU-RMP and the local implementation of risk management activities, for example: any differences between the risk minimisation activities undertaken as reflected in the content of the Global/EU Summary of Product

Characteristics (SmPC) and the proposed Zambian Product Information (PI), and the reasons for the difference. This will allow the Authority to assess the appropriateness of the proposed RMP in the Zambian environment.

i. Purpose of the Zambia Specific Annex

The Zambia Specific Annex should provide Zambia specific information that is important in assessing the 'risk' in Zambia (and therefore appropriateness of proposed plans/activities), the relevance of safety monitoring and risk management activities in Zambia and identify and explain the reasons for any differences with activities planned in the EU.

ii. Content of Zambia Specific Annex

The Annex should include:

a) Differences in indications between the Global/European Union (EU) and Zambia if applicable.
b) Zambia specific epidemiological information on the population to be treated. (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 Zambian population).
c) Zambia information, on potential for medication errors or other risks.

d) Applicability of EU activities to the Zambian environment if no specific Zambian data will be collected.

iii. Format of Zambia Specific Annex

A recommended format for the Zambia Specific Annex is as below.

a) Introduction - Purpose of Zambia Specific Annex.
b) Pharmacovigilance practice - Routine pharmacovigilance systems in Zambia and studies referenced in the RMP. Describe involvement of Zambia and applicability of global studies to the Zambian environment, or—if not applicable or relevant to the Zambian environment—include a justification.
c) Risk minimisation plan - Address how risk minimisation activities will be implemented and evaluated in Zambia. If surveys or studies are referenced in the Zambia Specific Annex, copies of outlines and protocols should be provided.

   Provide a justification if activities in the EU are not to be implemented in Zambia. Indicate how and when evaluation of risk minimisation activities, including educational activities, will be undertaken. MAH 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.

d) Contact person for RMP - This is the person the MAH considers responsible for the implementation of the RMP activities in Zambia and will be the local QPPV.

Principles for assessment of risk management plans

The principle points which need to be considered when preparing or reviewing a risk management plan for a medicine or allied substance are:

Safety specification

a. Have all appropriate parts of the safety specification been included?
b. Have all appropriate data been reviewed when compiling the safety specification, i.e. are there important (outstanding) issues from other sections of the dossier which have not been discussed in the safety specification?
c. If parts of the target population have not been studied, have appropriate safety concerns in relation to potential risks and missing information been included?
d. What are the limitations of the safety database and what reassurance does it provide regarding the safety profile of the medicine or allied substance?

e. Are there specific risks in addition to those addressed under ICH-E2E, e.g. off-label use, misuse and abuse, transmission of infectious disease, medication error, etc.?

f. Does the safety specification provide a true reflection of the safety concerns (i.e. important identified risks, important potential risks and missing information) with the product?

g. If a generic or hybrid application, have all safety concerns from the reference medicine or allied substance been included in the safety specification? Does its place in the therapeutic armamentarium as described concur with the intended indication and current medicinal practice?

Pharmacovigilance (Safety monitoring) Plan

a. Are all safety concerns from the safety specification covered in the pharmacovigilance plan?

b. Are routine pharmacovigilance activities adequate or are additional pharmacovigilance activities necessary?

c. Are the activities in the pharmacovigilance plan clearly defined and described and suitable for identifying or characterising risks or providing missing information?

d. Are the safety studies which have been imposed by the Authority as conditions clearly identified?
e. If medication error is a safety concern, does the RMP include appropriate proposals to monitor these?
f. Are the proposed additional studies necessary and/or useful?
g. When draft protocols are provided, are the proposed studies in the pharmacovigilance plan adequate to address the scientific questions and are the studies feasible?
h. Are appropriate timelines and milestones defined for the proposed actions, the submission of their results and the updating of the pharmacovigilance plan?
i. Plans for post-authorisation studies on efficacy
j. Does the description of the efficacy of the product and what studies and endpoints it was based on conform with the contents of the dossier?
k. Do all proposed studies have a valid scientific question as their primary aim and are any designed to increase use of the product?
l. Risk minimisation measures
m. Does the product information adequately reflect all important identified risks and missing information?

n. Are any potential risks sufficiently relevant to the safe and effective use of the product that information about them should be included in the product information?
o. Is the proposed wording about the risks and location in the product information appropriate and in line with relevant guidelines?
p. Has the MAH considered ways to reduce medication errors?
q. Has this been translated into appropriate product information (including device design where appropriate) and pack design?
r. Are proposed risk minimisation activities appropriate and adequate?
s. Have additional risk minimisation activities been suggested and if so, are they risk proportionate and adequately justified?
t. Are the methodologies for measuring and assessing the effectiveness of risk minimisation activities well described and appropriate?
u. Have criteria for evaluating the success of additional risk minimisation activities been defined as a priori?

Summary of the Risk Management Plan

a. Is it a true representation of the RMP?
b. Have the facts been presented appropriately

c. Are the content, format and language suitable for the intended audience?
d. Have all required formats been provided?

When an update is being assessed

a. Have new data been incorporated into the safety specification?
b. Have appropriate changes been made to the pharmacovigilance plan (if necessary, in the light of new data)?
c. Is there an evaluation of the effectiveness of risk minimisation measures?
d. Have appropriate changes to risk minimisation measures been proposed if necessary?
e. Does the new data suggest that a formal evaluation of the benefit-risk balance (if not already done in a PSUR/PBRER) is needed?

Quality management systems and record management

i. Although many experts may be involved in writing the RMP, the final responsibility for its quality, accuracy and scientific integrity lies with the Marketing Authorisation Holder. As such the qualified person responsible for pharmacovigilance in Zambia (LQPPV) should be aware of and have sufficient Authority over the content. The MAH is responsible for updating the RMP when new

information becomes available and should apply the quality principles detailed in Section 2.

ii. The MAH should maintain records of when RMPs were submitted to the Authority and the significant changes between each version of the RMP. These records, the RMPs and any documents relating to information within the RMP may be subject to audit and inspection by the Authority.

5. SAFETY COMMUNICATION

5.1. Communicating safety information to patients and healthcare professionals is a public health responsibility and is essential for achieving the objectives of safety monitoring in terms of promoting the rational, safe and effective use of medicines and allied substances, preventing harm from adverse reactions and contributing to the protection of patients and public health. This section provides guidance to MAHs on how to communicate and coordinate safety information in Zambia.

5.2. Safety communication is a broad term covering different types of information on medicines and allied substances, including statutory information as contained in the product information [i.e. the summary of product characteristics (SmPC), package leaflet (PL) and the labelling of the packaging] and public assessment reports.

5.3. This section focuses on the communication of 'new or emerging safety information', which means new information about a previously known or unknown risk of a medicine or allied substance which has or may have an impact on a medicine or allied substance's benefit-risk balance and its condition of use.

5.4. Unless otherwise stated, the term 'safety communication' should be read as referring to emerging safety information.

High levels of public interest are anticipated when new safety concerns arise, and it is important that clear and consistent messages are provided in a timely manner. Communication of important new safety information on medicines and allied substances should consider the views and expectations of concerned parties, including patients and healthcare professionals.

5.5. Objectives for safety communication

5.5.1. Safety communication aims at:

a. Providing timely, evidence-based information on the safe and effective use of medicines and allied substances;
b. Facilitating changes to healthcare practices (including self- medication practices) were necessary;
c. Changing attitudes, decisions and behaviours in relation to the use of medicines and allied substances;
d. Supporting risk minimisation behaviour;
e. Facilitating informed decisions on the rational use of medicines and allied substances.

5.5.2. In addition to the above, effective high-quality safety communication can support public confidence in the regulatory system.

5.6. Principles of safety communication

5.6.1. The following principles of safety communication should be applied:

a. The need for communicating safety information should be considered throughout the safety monitoring and risk management process and should be part of risk assessment.

b. There should be adequate coordination and cooperation between the different parties involved in issuing safety communications (e.g. the Authority, other public bodies and MAHs).

c. Safety communication should deliver relevant, clear, accurate and consistent messages and reach the right audience at the right time for them to take appropriate action.

d. Safety communication should be tailored to the appropriate audiences (e.g. patients and healthcare professionals) by using appropriate language and taking account of the different levels of knowledge and information needs whilst maintaining the accuracy and consistency of the information conveyed.

e. Information on risks should be presented in the context of the benefits of the medicine or allied substances and include available and relevant information on

seriousness, severity, frequency, risk factors, time to onset, reversibility of potential adverse reactions and, if available, expected time to recovery.

f. Safety communication should address the uncertainties related to a safety concern. This is of relevance for emerging information which is often communicated while the Authority is conducting its evaluations; the usefulness of communication at this stage needs to be balanced against the potential for confusion if uncertainties are not properly represented.

g. Information on competing risks such as the risk of non-treatment should be included where appropriate.

h. 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; for risk comparisons, denominators should be the same in size. The use of other tools such as graphical presentation of the risk and/or the benefit-risk balance may also be used.

i. 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.

j. 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.

k. The effectiveness of safety communication should be evaluated where appropriate and possible.

l. Safety communications should comply with relevant requirements relating to individual data protection and confidentiality.

5.7. Target audiences

5.7.1. The primary target audiences for safety communication issued by the Authority and MAHs should be patients/general public and/or healthcare professionals who use (i.e. prescribe, handle, dispense, administer or take) medicines and allied substances. As primary target audiences, healthcare professionals play an essential role. Effective safety communication enables them to give clear and useful information to their patients, thereby promoting patient safety and confidence in the regulatory system. Both healthcare professionals in clinical practice and those involved in clinical trials should be provided with appropriate information on any safety concern at the same time. Patient, consumer and healthcare professional organisations can play a role as multipliers as they can

disseminate important safety information to target audiences.

5.7.2. The media is also a target audience for safety communication. The capacity of the media to reach out to patients, healthcare professionals and the general public is a critical element for amplifying new and important information on medicines and allied substances. The way safety information is communicated through the media will influence the public's perception and it is therefore important that the media receives safety information directly from the Authority in addition to the information they receive from other sources, such as from the MAHs.

5.8. Content of safety communication

5.8.1. Safety communication should contain:

a. Important emerging information on any authorised medicine or allied substance which has an impact on the medicine or allied substance's benefit-risk balance under any conditions of use;
b. The reason for initiating safety communication is clearly explained to the target audience;
c. Any recommendations to healthcare professionals and patients on how to deal with safety concerns;

d. When applicable, a statement on the agreement between the MAH and the Authority on the safety information provided;
e. Information on any proposed change to the product information [e.g. the summary of product characteristics (SmPC) or package leaflet (PL)];
f. A list of literature references, when relevant or a reference to where more detailed information can be found; where relevant, a reminder of the need to report suspected adverse reactions in accordance with national spontaneous reporting systems.

5.8.2. The information on safety communication should not be misleading and should be presented objectively. Safety information should not include any material or statement which might constitute advertising.

5.9. Means of safety communication

Communication tools and channels have become more numerous and varied over time, offering the public more information than was previously possible. The use of this increasing variety of means should be considered when issuing safety communication to reach the target audiences and meet their growing expectations. Different communication tools and channels are discussed below:

5.9.1. Direct healthcare professional communication (DHPC)

5.9.1.1. Direct Healthcare Professional Communication (DHPC) is a communication to healthcare professionals by MAH or by a competent Authority, to inform them of the need to take certain actions or adapt their practices in relation to important new safety information for a medicine or allied substance.

5.9.1.2. DHPCs are not replies to enquiries from healthcare professionals, nor are they meant as educational material for routine risk minimisation activities. The preparation of DHPCs involves cooperation between the MAH and the Authority. Agreement between these two parties should be reached before DHPC is issued by the MAH. The agreement will cover both the content of the information and the communication plan, including the intended recipients and the timetable for disseminating the DHPC.

5.9.1.3. Where there are several MAHs of the same active substance for which a DHPC is to be issued, a single consistent message should normally be delivered. Whenever possible, it is advised that healthcare professionals' organisations or learned societies are involved as appropriate during the preparation of DHPCs to ensure that the information they deliver is

useful and adapted to the target audience. A DHPC may be complemented by other communication tools and channels and the principle of providing consistent information should apply. A DHPC may be an additional risk minimisation measure as part of a risk management plan.

5.9.1.4. A DHPC should be disseminated in the following situations when there is a need to take immediate action or change current practice in relation to a medicine or allied substance:

i. Suspension, withdrawal or revocation of a Marketing Authorisation for safety reasons;
ii. An important change to the use of a medicine or allied substance due to the restriction of an indication, a new contraindication, or a change in the recommended dose due to safety reasons;
iii. A restriction in availability or discontinuation of a medicine or allied substance with potential detrimental effects on patient care.

5.9.1.5. Other situations where dissemination of a DHPC should be considered are:

i. New major warnings or precautions for use in the product information

ii. New data identifying a previously unknown risk or a change in the frequency or severity of a known risk;

iii. Substantiated knowledge that the medicine or allied substance is not as effective as previously considered;

iv. New recommendations for preventing or treating adverse reactions or to avoid misuse or medication error with the medicine or allied substance;

v. Ongoing assessment of an important potential risk, for which data available at a particular point in time are insufficient to take regulatory action (in this case, the DHPC should encourage close monitoring of the safety concern in clinical practice and encourage reporting and possibly provide information on how to minimise the potential risk). The Authority may disseminate or request the MAH to disseminate a DHPC in any situation where the Authority considers it necessary for the continued safe and effective use of a medicine or allied substance.

5.9.2. Documents in lay language

5.9.2.1. Communication material in lay language (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. Lay language documents should contain the Authority's recommendations and advice for risk minimisation for patients and healthcare professionals in relation to safety concerns and should be accompanied by relevant background information.

5.9.2.2. Lay language documents are generally useful to members of the public who have an interest in the subject but do not have a scientific or regulatory background. Reference should be made to other communication materials on the topic to direct readers to where they can find further information.

5.9.2.3. Whenever possible, it is advised that patients and healthcare professionals are involved during the preparation of lay language documents to ensure that the information they deliver is useful and adapted to the target audience. Where the MAH needs to communicate to the general public, information may be translated into a local language. Local language translations should be appropriately certified.

5.9.3. Press communication

5.9.3.1. Press communication includes press releases and press briefings which are primarily intended for

journalists. The Authority may send press releases directly to journalists in addition to publishing them on their websites. This ensures that journalists, in addition to obtaining information from other sources, receive information that is consistent with the Authority's scientific assessment. Interaction with the media is an important way to reach out to a wider audience as well as to build trust in the regulatory system. Press releases may also be prepared and published by MAHs. Their press releases may reflect the position of the MAH on a safety topic but should also refer to any regulatory action taken by the Authority. Relevant ongoing reviews should be mentioned in any communication by the MAH.

5.9.3.2. Although aimed at journalists, press releases will be read by other audiences such as healthcare professionals, patients and the general public. Reference should therefore be made to related communication materials on the topic. In cases where a DHPC is also prepared, healthcare professionals should ideally receive it prior to/or around the same time as the publication or distribution of a press release so that they are better prepared to respond to patients.

5.9.4. Website

A website is a key tool for members of the public (including patients and healthcare professionals) actively searching the internet for specific information on medicines and allied substances. MAHs should ensure that important safety information published on websites under their control is easily accessible and understandable by the public. Information on websites should be kept up to date, with any information that is out-of-date marked as such or removed.

5.9.5. Other web-based communications

Online safety information may also be disseminated via other web tools. When using newer, more rapid communication channels, special attention should be paid to ensure that the accuracy of the information released is not compromised. Communication practices should consider emerging communication tools used by the various target audiences.

5.9.6. Bulletins and newsletters

Bulletins and newsletters provide at regular intervals new information about medicines and allied substances and their safety and effectiveness. MAHs can reach a large audience with these tools by using web- based and other available means.

5.10. Responding to enquiries from the public

MAHs should have systems in place for responding to enquiries about medicines and allied substances from individual members of the public. Responses should consider the information which is in the public domain and should include the relevant recommendations to patients and healthcare professionals issued by the Authority. Where questions relate to individual treatment advice, the patient should be advised to contact a healthcare professional.

5.11. Other means of communication

5.11.1. In addition to those discussed above, there are other tools and channels such as publications in scientific journals and journals of professional bodies.

5.11.2. Some tools and channels may be used in the context of risk management; risk minimisation measures often include specific programmes for risk communication.

5.12. Effectiveness of safety communication

5.12.1. Safety communication is considered effective when the message transmitted is received and understood by the target audience in the way it was intended, and appropriate action is taken by the target audience. Adequate feedback mechanisms have been introduced

to measure the effectiveness of communication based on clear objectives. Measuring effectiveness allows lessons to be learnt and helps in making decisions on prioritising and adapting tools and practices to meet the needs of the target audience. A research-based approach will normally be appropriate to establish that safety communications have met the standard set out under the principles of safety communication. This approach may measure different outcomes, including behaviour, attitudes, and knowledge. When evaluating the effectiveness of safety communication, the scope of the evaluation may be broadened to include factors other than the performance of the individual tools used in the safety communication.

5.12.2. In the case of DHPCs, the MAH should be responsible for evaluating the dissemination of the DHPCs they prepare and should inform the Authority of the outcome and of any difficulties identified (e.g. problems related to the list of recipients or the timing and mechanism of dissemination). Appropriate action should be taken as needed to correct the situation or prevent similar problems in the future.

5.13. Quality management system requirements for safety communication

5.13.1. In accordance with the quality management system requirements, procedures should be in place to ensure that safety communications comply with the principles of safety communication as appropriate.

5.13.2. In particular, the communications should be subject to quality controls to ensure their accuracy and clarity. For this purpose, reviewed procedures with allocated responsibilities should be followed and documented.

5.14. Notification of Safety communication

5.14.1. MAH should notify the Authority of their intention to disseminate safety communication to healthcare professionals or the general public.

5.14.2. The MAH may coordinate with the Authority in the preparation or dissemination of the safety communication.

5.14.3. The MAH should receive positive feedback from the Authority before the communication can be disseminated.

6. ADVERSE EVENT REPORTING

6.1. This Section addresses the requirements for MAHs as regards the collection, data management and reporting of suspected adverse reactions (serious and non-serious) associated with medicines and allied substances granted Marketing Authorisation in Zambia.

6.2. All reports are to be submitted to the Authority via e-reporting, Med Safety App or as hard copy reports. Non-serious reports should be submitted within 30 calendar days, while serious adverse reaction:

6.2.1. that results in death, within seven calendar days of becoming aware of the adverse reaction or adverse event; or

6.2.2. that does not result in death, within fifteen calendar days of becoming aware of the adverse reaction or adverse event.

6.3. Reports of adverse events occurring in special situations should be submitted within 15 calendar days of becoming aware.

6.4. Structures and processes

This section highlights the general principles in relation to the collection, recording and reporting of reports of suspected

adverse reactions associated with medicines and allied substances as it concerns the MAHs.

6.4.1. **Collection of reports**

i. The MAH should take appropriate measures to collect and collate all reports of suspected adverse reactions associated with medicines and allied substances originating from unsolicited or solicited sources. The Safety Monitoring System should be designed so that it helps to ensure that the collected reports are authentic, legible, accurate, consistent, verifiable and as complete as possible for their clinical assessment and submission to the Authority.

ii. The system should ensure the collection and recording of all reports of suspected adverse reactions brought to its attention by health care professionals or consumers or occurring in the context of post- authorisation study. MAHs should consider all reports including those of suspected adverse reactions received from patients and the general public.

iii. MAHs should establish mechanisms enabling the traceability and follow-up of adverse reaction reports while complying with data protection principles. It is recommended that safety monitoring data and documents relating to individual authorised medicines

and allied substances should be retained if the product is authorised and for at least 10 years after the Marketing Authorisation has ceased to exist.

iv. With regards to the collection and recording of reports of suspected adverse reactions, MAH's responsibilities apply to reports related to medicines and allied substances for which ownership cannot be excluded on the basis of one of the following criteria: medicine or allied substance name, active substance name, pharmaceutical form, batch number or route of administration.

v. The MAH shall ensure that any information on adverse reactions, suspected to be related to at least one of the active substances of its medicines and allied substances authorised in Zambia, is brought to its attention by any company outside the country belonging to the same mother company (or group of companies). The same applies to the MAH when having concluded a commercial agreement with a company outside Zambia for one of its medicines or allied substances authorised in the country. The clock for reporting starts when a valid ICSR is first received by one of these companies outside the country.

vi. All notifications that contain safety monitoring data should be recorded and archived in compliance with the applicable data protection requirements.

6.4.2. Unsolicited/Spontaneous reports

i. A spontaneous report is an unsolicited communication by a healthcare professional, or consumer that describes one or more suspected adverse reactions in a patient who was given one or more medicines or allied substances and that does not derive from a study or any organised data collection systems where adverse events reporting is actively sought.

ii. Stimulated reporting that occurs consequent to a direct healthcare professional communication, publication in the press, questioning of healthcare professionals by company representatives, communication from patients' organisations to their members, or class action lawsuits should be considered spontaneous reports.

iii. Unsolicited consumer adverse reactions reports should be handled as spontaneous reports irrespective of any subsequent "medical confirmation".

iv. MAHs shall record all reports of suspected adverse reactions originating from within Zambia, which are brought to their attention spontaneously by healthcare professionals, or consumers. In this context, MAHs

may consider utilising their websites to facilitate the collection of reports of suspected adverse reactions by providing adverse reactions forms for reporting, or via e-reporting or appropriate contact details for direct communication.

6.4.3. Literature reports

i. The scientific and medical literature is a significant source of information for the monitoring of the safety profile and of the benefit-risk balance of medicines and allied substances, particularly in relation to the detection of new safety signals or emerging safety issues. MAHs are therefore expected to maintain awareness of possible publications through a systematic literature review of widely used reference databases (e.g. Medline, Excerpta Medica or Embase) at regular intervals. The MAH should ensure that the literature review includes the use of reference databases that contain the largest reference of articles in relation to the medicine or allied substance properties. In addition, MAHs should have procedures in place to monitor scientific and medical publications in local journals in countries where medicines and allied substances have a Marketing Authorisation, and to bring them to the attention of the Authority as appropriate.

ii. Reports of suspected adverse reactions from scientific and medical literature, including relevant published abstracts from meetings and draft manuscripts, should be reviewed and assessed by MAH to identify and record ICSRs originating from spontaneous reports or non-interventional post-authorisation studies.

iii. If multiple medicines and allied substances are mentioned in the publication, only those that are identified by the publication's author(s) as having at least a possible causal relationship with the suspected adverse reaction should be considered by the concerned MAHs.

iv. One case should be created for each single patient identifiable based on characteristics provided in sections 6.4.15 to 6.4.16. Relevant medical information should be provided, and the publication author(s) should be considered as the primary source(s).

6.4.4. **Reports from other sources**

If MAH becomes aware of a report of suspected adverse reactions originating from a non-medical source, for example the lay press or other media, it should be handled as a spontaneous report. Every attempt should be made to follow up the case to obtain the minimum information that constitutes a valid

ICSR. The same reporting time frames should be applied as for other spontaneous reports.

6.4.5. **Information on suspected adverse reactions from the internet or digital media**

i. MAHs should regularly screen internet or digital media under their management or responsibility, for potential reports of suspected adverse reactions. In this aspect, digital media is company sponsored if it is owned, paid for and/or controlled by the MAH. The frequency of the screening should allow for potential valid ICSRs to be reported to the Authority within the appropriate reporting timeframe. MAH may also consider utilising their websites to facilitate the collection of reports of suspected adverse reactions.

ii. If MAH becomes aware of a report of suspected adverse reaction described in any non-company sponsored digital medium, the report should be assessed to determine whether it qualifies for reporting.

iii. Unsolicited cases of suspected adverse reactions from the internet or digital media should be handled as spontaneous reports. The same reporting time frames as for spontaneous reports should be applied.

iv. In relation to cases from the internet or digital media, the identifiability of the reporter refers to the existence of a real person, that is, it is possible to verify the contact details of the reporter (e.g., an email address under a valid format has been provided). If the country of the primary source is missing, the country where the information was received, or where the review took place, should be used as the primary source country.

6.4.6. Solicited reports

i. Solicited reports of suspected adverse reactions are those derived from organised data collection systems, which include clinical trials, non- interventional studies, registries, post-approval named patient use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers, compassionate use or name patient use, or information gathering on efficacy or patient compliance. Reports of suspected adverse reactions obtained from any of these data collection systems should not be considered spontaneous.

ii. To ensure safety reporting, solicited reports should be classified as study reports, and should have an appropriate causality assessment, to consider whether

they refer to suspected adverse reactions and therefore meet the criteria for reporting.

6.4.7. MAH initiated post-authorisation studies

MAHs should record all reports of suspected adverse reactions originating from within or outside Zambia, which occur in post-authorisation studies, initiated, managed, or financed by them. For all solicited reports, MAHs should have mechanisms in place to record and document complete and comprehensive case information and to evaluate that information, to allow meaningful assessment of individual cases and reporting of valid ICSRs related to the studied (or supplied) medicine or allied substance. MAHs should therefore exercise due diligence in establishing such a system, by following up with those reports and seeking the view of the primary source as regards the causal role of the studied (or supplied) medicine or allied substance on the notified adverse event. Where this opinion is missing, the MAH should exercise its own judgement based on the information available to decide whether the report is a valid ICSR, which should be reported to the Authority. This requirement does not apply to study designs based on secondary use of data since reporting of ICSRs is not required.

6.4.8. Adverse Reaction Reports from Post-Registration Studies

i. MAHs should report all known serious, suspected ARs occurring in post-registration studies undertaken in Zambia, of which the MAH is aware, in accordance with reporting time frames for serious ARs. MAHs should have mechanisms in place to collect full and comprehensive case information and to evaluate that information to allow meaningful assessment of individual cases and reporting of valid ARs related to the studied (or supplied) medicine.

ii. MAHs should therefore exercise due diligence in establishing such a system; in following up those reports; and in seeking the view of the primary source regarding the causal role of the studied (or supplied) medicine in the notified AE. Where the primary source's opinion as to the causal role is missing, the MAH should exercise its own judgement based on the information available to decide whether the report is a valid AR that must be reported to the Authority in accordance with the requirements described in this document.

iii. In instances where the post-registration study is conducted or initiated by an investigator, independent of the MAH of the medicine, the responsibility for

reporting ARs to the Authority rests with the investigator. However, if the MAH is aware of the study, the MAH should request that it is notified by the investigator of serious ARs that occur in the study. Where MAH becomes aware of such ARs, they must ensure that the ARs are reported in accordance with the requirements described in this document.

6.4.9. **Reports from other Post-Marketing Initiatives: Surveys, Registries etc.**

i. MAHs may be involved in post-marketing initiatives that result in the collection of information related to their products such as patient support and disease management programs, surveys of patients or healthcare providers, information gathering on efficacy or patient compliance, market research programs and voluntary patient registries. These activities may involve the receipt of information on AEs.

ii. MAHs should have in place a system to collect full and comprehensive case information and to evaluate that information to determine whether the collected AEs are possibly related to the studied (or supplied) medicine. If so, they should be classified and processed as suspected ARs and are subject to the reporting requirements described in this document.

6.4.10. **Special situations**

i. Use of a medicine or allied substance during pregnancy or breastfeeding

a) Pregnancy

(i) Reports, where the embryo or foetus may have been exposed to medicines and allied substances (either through maternal exposure or paternal exposure), should be followed up to collect information on the outcome of the pregnancy and development of the child after birth. When an active substance (or one of its metabolites) has a long half-life, this should be considered when assessing the possibility of exposure of the embryo, if the medicine or allied substance was taken before conception.

(ii) Not infrequently, pregnant women or healthcare professionals will contact either the Authority or the MAH to request information on the teratogenicity of a medicinal product and/or experience of use during pregnancy. Reasonable attempts should be made to obtain information on any possible medicine or allied substance exposure to an embryo or foetus and to follow-up on the outcome of the pregnancy.

(iii) Reports of exposure to medicines and allied substances during pregnancy should contain as

many detailed elements as possible to assess the causal relationships between any reported adverse events and the exposure to the suspected medicine or allied substance. In this context the use of standard structured questionnaires is recommended.

(iv) Individual cases with an abnormal outcome associated with a medicine or allied substance following exposure during pregnancy are classified as serious reports and should be reported, in accordance with the requirements outlined in section 6.4.12.

(v) This especially refers to:

a. Reports of congenital anomalies or developmental delay, in the foetus or the child;
b. Reports of foetal death and spontaneous abortion; and
c. Reports of suspected adverse reactions in the neonate that are classified as serious.

(vi) Other cases, such as reports of induced termination of pregnancy without information on congenital malformation, reports of pregnancy exposure without outcome data or reports which have a normal outcome, should not be reported since there is no suspected adverse reaction. These reports

should however be collected and discussed in the periodic safety update reports.

(vii) However, in certain circumstances, reports of pregnancy exposure with no suspected reactions may need to be reported. This may be a condition of the Marketing Authorisation stipulated in the risk management plan; for example, pregnancy exposure to medicines and allied substances contraindicated in pregnancy or medicines and allied substances with a special need for surveillance because of a high teratogenic potential (e.g. thalidomide, isotretinoin).

(viii) A signal of a possible teratogen effect (e.g. through a cluster of similar abnormal outcomes) should be notified immediately to the Authority.

b) Breastfeeding

Suspected adverse reactions which occur in infants following exposure to a medicine or allied substance from breast milk should be reported to the Authority.

ii. Use of a medicine or allied substance in a children and elderly population

a) The collection of safety information in the children or elderly population is important. Reasonable attempts should therefore be made to obtain and submit the age or age group of the patient when a case is reported by a healthcare professional, or consumer, to be able to identify potential safety signals specific to a particular population.

iii. Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure

a) In this guideline, medication error refers to any unintentional error in the prescribing, dispensing, or administration of a medicine or allied substance while in the control of healthcare professional or consumer.

b) Reports of overdose, abuse, off-label use, misuse or occupational exposure with no associated adverse reaction should not be reported as ICSRs. They should be considered in periodic safety update reports as applicable. When those reports constitute safety issues impacting on the benefit-risk balance of the medicine or allied substance, they should be notified to the Authority in accordance with the recommendations provided in section 6.4.11.

c) Reports associated with suspected adverse reactions should be routinely followed to ensure that the information is as complete as possible with regards to the symptoms, treatments, outcomes, context of occurrence (e.g., error prescription, administration, dispensing, dosage, unauthorised indication or population, etc.).

d) In the case of a medication error, a case report should be submitted to the Authority regardless of whether a patient has been harmed or not.

iv. Lack of therapeutic efficacy

a) Reports of lack of therapeutic efficacy should be reported within 15 calendar days and followed up if incomplete unless the reporter has specifically stated that the outcome was due to disease progression and was not related to the medicine or allied substance.

b) Clinical judgment should be used when reporting cases of lack of therapeutic efficacy. For example, an antibiotic used in a life-threatening situation where the medicine or allied substance was not in fact appropriate for the infective agent should not be reported as such (refer to section on medication error). However, a life-threatening infection, where the lack of therapeutic efficacy appears to be due to the development of a

newly resistant strain of a bacterium previously regarded as susceptible, should be reported within 15 days.

c) For vaccines, cases of lack of immunogenic effect should be reported, with the view to highlight potential signals of reduced immunogenicity in a sub-group of vaccinees, waning immunity, or strain replacement. Regarding the latter, it is considered that spontaneously reported cases of lack of immunogenic effect by a healthcare professional may constitute a signal of strain replacement. Such a signal may need prompt action and further investigation through post-authorisation safety studies as appropriate. General guidance regarding the monitoring of vaccines' failure, provided in the Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance, may be followed.

v. Suspected adverse reactions related to quality defect or Substandard and falsified medicines and allied substances

a) Reports of suspected adverse reactions associated with a suspected or confirmed substandard and falsified medicine or allied substance of a valid ICSR should be reported. The seriousness of the ICSR is linked to the seriousness of the reported suspected adverse reactions

in accordance with the definitions provided in the definition.

b) In addition, to protect public health, it may become necessary to implement urgent measures such as the recall of one or more defective batch(es) of a medicine or allied substance from the market. Therefore, MAHs should have a system in place to ensure that reports associated with substandard or falsified medicines and allied substances are investigated in a timely fashion and that confirmed substandard and falsified products are notified separately by the Authority.

vi. Suspected transmission via a medicine or allied substance of an infectious agent

a) For the purposes of reporting, any suspected transmission of an infectious agent via a medicine or allied substance should be considered as a serious adverse reaction and such cases should be reported within 15 days. This also applies to vaccines. If no other criterion is applicable, the seriousness of this ICSR should be considered as an important medical event.

b) In the case of medicines and allied substances derived from human blood or human plasma, haemovigilance

procedures may also apply. Therefore, the MAH should have a system in place to communicate suspected transmission via a medicine or allied substance of an infectious agent to the manufacturer, the relevant blood establishment(s) and the Authority. Any organism, virus or infectious particle (e.g. prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

c) The transmission of an infectious agent may be suspected from clinical signs or symptoms, or laboratory findings indicating an infection in a patient exposed to a medicine or allied substance. Emphasis should be on the detection of infections/infectious agents known to be potentially transmitted via a medicine or allied substance, but the occurrence of unknown agents should also always be considered.

d) In the context of evaluating a suspected transmission of an infectious agent via a medicine or allied substance, care should be taken to discriminate, whenever possible, between the cause (e.g. injection/ administration) and the source (e.g. contamination) of the infection and the clinical conditions of the patient at the time of the infection (immuno- suppressed /vaccinee).

e) Confirmation of contamination (including inadequate inactivation/attenuation of infectious agents as active substances) of the concerned medicine or allied substance increases the evidence for transmission of an infectious agent and may therefore be suggestive of a quality defect for which the procedures detailed in section 6.4.10 should be applied.

6.4.11. **Clusters**

i. Emerging safety issues

Events may occur, which do not fall within the definition of reportable valid ICSRs, and thus are not subject to the reporting requirements, even though they may lead to changes in the known benefit-risk balance of a medicine or allied substance and/or impact on public health. These events/observations, which may affect the benefit-risk balance of a medicine or allied substance, are not to be submitted as ICSRs. They should be notified of emerging safety issues by writing to the Authority at least within 30 days of becoming aware of them. The document should indicate the points of concern and the actions proposed in relation to the marketing application/authorisation for the medicine concerned or allied substance. Those safety issues should also be analysed in the relevant sections of the

periodic safety update report of the authorised medicine or allied substance.

ii. Period between the submission of MA application and the grant of the MA

In the period between the submission of the Marketing Authorisation application and the granting of the Marketing Authorisation, information (quality, non-clinical, clinical) that could impact on the benefit-risk balance of the medicine or allied substance under evaluation may become available to the applicant. It is the responsibility of the applicant to ensure that this information is immediately submitted to the Authority.

iii. Period after suspension, revocation or withdrawal of MA

Where a Marketing Authorisation is suspended, withdrawn or revoked, the former MAH is encouraged to continue to collect spontaneous reports of suspected adverse reactions originating within the country to facilitate the review of delayed onset adverse reactions or of retrospectively notified cases.

iv. Public health emergency or other health threat

A public health emergency is a public health threat duly declared by the ministry responsible for health. In the event of a public health emergency or other health threat, regular reporting requirements may be amended. Such arrangements will be considered on a case-by-case basis and will be appropriately notified by the Authority.

ICSRs involving a medicine or allied substance being used to address a condition related to the declared public health emergency or other health threat should be submitted to the Authority in an expedited manner but no later than 15 calendar days.

v. Reports on patient support programmes and market research programmes

Safety reports originating from patient support and market research programmes should be considered as solicited reports. The MAHs should have the same mechanisms in place as for all other solicited reports to manage that information and report valid cases of adverse reactions, which are suspected to be related to the concerned medicine or allied substance.

6.4.12. **Report on Individual case safety reports (ICSRs)**

i. Only valid ICSRs should be reported. The clock for the reporting of a valid ICSR starts as soon as the information containing the minimum reporting criteria has been brought to the attention of the MAH, including medical representatives and contractors. This date should be considered as day zero. It is the first day when a receiver gains knowledge of a valid ICSR, irrespective of whether the information is received during a weekend or public holiday. Reporting timelines are based on calendar days.

ii. Where the MAH has set up contractual arrangements with a person or an organisation, explicit procedures and detailed agreements should exist between the MAH and the person/organisation to ensure that the MAH can comply with the reporting obligations. These procedures should specify the processes for exchange of safety information, including timelines and regulatory reporting responsibilities and should avoid duplicate reporting to the Authority.

iii. For ICSRs described in the scientific and medical literature, the clock starts (day zero) with awareness of a publication containing the minimum information for reporting. Where contractual arrangements are made with a person/organisation to perform literature

searches and/or report valid ICSRs, detailed agreements should exist to ensure that the MAH can comply with the reporting obligations.

iv. When additional significant information is received for a previously reported case, the reporting time clock starts again for the submission of a follow-up report from the date of receipt of the relevant follow- up information. For reporting, significant follow-up information corresponds to new medical or administrative information that could impact on the assessment or management of a case or could change its seriousness criteria; non-significant information includes updated comments on the case assessment or corrections of typographical errors in the previous case version.

6.4.13. Reporting time frames for Serious Adverse Reactions

i. The MAH and other persons authorised to distribute medicines, and allied substances should keep records of all suspected serious adverse reactions which have occurred in Zambia and brought to their attention and report the same to the Authority not later than fifteen (15) days following the receipt of information.

However, reports that result in death, should be reported within seven days of becoming aware of the report.

ii. All serious ARs must be reported as soon as possible and in no case later than fifteen (15) calendar days from receipt by the MAH. The clock for serious ARs starts (as day 0) on the day that the four minimum data elements in relation to the AR report are received.

iii. The reporting time clock is considered to begin again when MAH receives additional clinical or medically relevant information for a previously reported serious AR. This information must be reported as soon as possible and in no case later than fifteen (15) calendar days after receipt of the additional information.

iv. If MAH receives additional information about a case initially classified as non-serious that indicates the case should be re-classified (e.g. from non-serious to serious), the MAH must report the case as soon as possible, and in no case later than 15 calendar days after receipt of the information that led to the change in classification.

v. For suspected serious AR cases occurring in Zambia that are identified through screening the worldwide literature, the clock starts (day zero) when the MAH becomes aware of a publication containing the four minimum data elements. It is preferable that a copy of

the relevant published article (in English or an English summary/translation) is provided to the Authority at the time the initial AR report is made. However, if the article is not available at this time, it must be provided to the Authority within 15 calendar days of submission of the AR report. Where difficulty is experienced in meeting the 15 calendar days requirement for submission of the article, the Authority must be notified in writing prior to the 15-day period ending.

vi. The MAH should report to the Authority any action relating to their product safety that has been taken by a regulatory Authority outside Zambia, including the basis for such action, not later than seven (7) days of first knowledge.

6.4.14. **Reporting timeframes for significant safety issues**

i. Any significant safety issues identified by the MAH must be reported to the Authority within seven (7) days. The seven (7) day clock starts from the time of awareness of the issue by the MAH. This is considered to have occurred when the MAH's review and analysis have been completed and a conclusion is drawn that is a significant safety issue, or when the MAH becomes aware of the actions of an overseas regulatory Authority.

ii. These situations are different from the reporting of individual ARs, where the MAH is allowed for up to 15 days to confirm and follow-up details before submitting an individual serious AR report to the Authority.

Tabulated summary of reporting requirements

Post registration ADR reports (registered medical products)

Type of ADR report	**Timeframe for reporting**	**Format**
Local Reports (Spontaneous/Published/Study) Serious (with fatal outcome) Serious (with no fatal outcome) Non serious (Unexpected) Non serious (Expected)	 7 days 15 days 15 days Within 30 days	 ADR form#
Foreign Reports (Spontaneous/published/study): Serious	On request or relating to specific safety issue	As guided by the Authority
Notification of change in nature, severity or frequency or risk factors	15 days	Detailed report (including publications)
New information impacting on benefit-risk profile of a product including international regulatory decisions	7 days	Detailed report (including publications)

The Authority's ADR report form or CIOMS form.

6.4.15. **Reporting format**

i. All adverse reactions should be reported using the adverse reaction reporting form available from the Authority. Alternatively, the MAH may use CIOMS reporting form. Discharge summaries, post- mortem reports, relevant laboratory data and other additional clinical data should be attached.

ii. Electronic submissions may also be required by the Authority using the ICH-E2B format for electronic reporting or any other format prescribed by the Authority.

6.4.16. **Validation of reports**

i. Only valid ICSRs qualify for reporting. All reports of suspected adverse reactions should therefore be validated before reporting them to the Authority to make sure that the minimum criteria for reporting are included in the reports (see ICH-E2D). These are:

a) One or more identifiable reporter (primary source) is characterised by qualification (e.g. pharmacist, physician, other healthcare professional, consumer or other non- healthcare professional) name, initials or address. Whenever possible, contact details for the reporter should be recorded so that follow-up activities

can be performed. However, if the reporter does not wish to provide contact details, the ICSR should still be considered as valid providing the organisation who was informed of the case was able to confirm it directly with the reporter. All parties providing case information or approached for case information should be identifiable, not only the initial reporter.

b) One single identifiable patient characterised by initials, patient identification number, date of birth, age, age group or gender. The information should be as complete as possible.

c) One or more suspected substance/medicine or allied substance (see the glossary).

d) One or more suspected adverse reaction (see the definitions).

ii. The report does not qualify as a valid ICSR in the following situations:

a) If the primary source has made an explicit statement that a causal relationship between the medicine or allied substance and the adverse event has been excluded and the MAH agrees with this, the report does not qualify as a valid ICSR since the minimum information is incomplete (There is no suspected adverse reaction).

b) The report does not also qualify as a valid ICSR if it is reported that the patient experienced an unspecified adverse reaction and there is no information provided on the type of adverse reaction experienced.

c) Similarly, the report is not valid if only an outcome (or consequence) is notified and

(i) no further information about the clinical circumstances is provided to consider it as a suspected adverse reaction, or

(ii) the primary source has not indicated a possible causal relationship with the suspected medicine or allied substance.

- For instance, MAH is made aware that a patient was hospitalised or died, without any further information. In this situation, medicinal judgment should always be applied in deciding whether the notified information is an adverse reaction or an event. For example, a report of sudden death would usually need to be considered as a case of suspected adverse reaction and reported.

iii. The lack of any of these four elements means that the case is considered incomplete and does not qualify for reporting. The MAH is required to exercise due

diligence in following up the case to collect the missing data elements. Reports, for which the minimum information is incomplete, should nevertheless be recorded within the Safety Monitoring System for use in on-going safety evaluation activities.

iv. When collecting reports of suspected adverse reactions via the internet or digital media, the term "identifiable" refers to the possibility of verification of the existence of a reporter and a patient.

v. When the MAH is made aware that the primary source may also have reported the suspected adverse reaction to another party concerned, the report should still be considered as a valid ICSR. All the relevant information necessary for the detection of the duplicate case should be included in the ICSR.

vi. A valid case of suspected adverse reaction initially submitted by a consumer cannot be downgraded to a report of non-related adverse event if the contacted healthcare professional (nominated by the consumer for follow-up information) disagrees with the consumer's suspicion. In this situation, the opinions of both the consumer and the healthcare professional should be included in the ICSR.

vii. For solicited reports of suspected adverse reactions, where the receiver disagrees with the reasonable

possibility of causal relationship between the suspected medicine or allied substance and the adverse reaction expressed by the primary source, the case should not be downgraded to a report of non-related adverse event. The opinions of both the primary source and the receiver should be recorded in the ICSR.

viii. The same principle applies to the ICSR seriousness criterion, which should not be downgraded from serious to non-serious if the MAH disagrees with the seriousness reported by the primary source.

6.4.17. **Follow-up of reports**

i. When first received, the information in suspected adverse reactions reports may be incomplete. These reports should be followed as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases. This is particularly relevant for monitored events of special interest, prospective reports of pregnancy, cases notifying the death of a patient, cases reporting new risks or changes in the known risks. This is in addition to any effort to collect missing minimum information. Any attempt to obtain follow-up information should be documented.

ii. Follow-up methods should be tailored towards optimising the collection of missing information. This

should be done in ways that encourage the primary source to submit new information relevant for the scientific evaluation of a particular safety concern. The use of targeted specific forms in the local language should avoid requesting the primary source to repeat information already provided in the initial report and/or to complete extensive questionnaires, which could discourage future spontaneous reporting. Therefore, consideration should be given to pre-populating some data fields in those follow-up report forms to make their completion by the primary source easy.

iii. When information is received directly from a consumer suggesting that an adverse reaction may have occurred, if the information is incomplete, attempts should be made to obtain consent to contact a nominated healthcare professional to obtain further follow-up information. When such a case, initially reported by a consumer, has been confirmed totally or partially) by a healthcare professional, this information should be clearly highlighted in the ICSR.

iv. For suspected adverse reactions relating to biological medicines and allied substances, the definite identification of the product concerned regarding its manufacturing is of particular importance. Therefore, all appropriate measures should be taken to clearly

identify the name of the product and the batch number. (Additonal information e.g. manufacturer etc.)

v. Clear written standard operating procedures should guarantee that the roles and responsibilities and the required tasks are clear to all parties involved and that there is provision for proper control and, when needed, change of system. This is equally applicable to activities that are contracted out to third parties, whose procedures should be reviewed to verify that they are adequate and compliant with applicable requirements.

6.4.18. **Data management**

i. Electronic data and paper reports of suspected adverse reactions should be stored and treated in the same way as other medical records with appropriate respect for confidentiality regarding patients' and reporters' identifiability. Confidentiality of patients' records including personal identifiers, if provided, should always be maintained. Identifiable personal details of reporting healthcare professionals should be kept confidential.

ii. To ensure safety monitoring data security and confidentiality, strict access controls should be applied to documents and to databases to authorised personnel only. This security extends to the complete data path. In

this respect, procedures should be implemented to ensure security and non-corruption of data during data transfer.

iii. When transfer of safety monitoring data occurs within an organisation or between organisations having concluded contractual agreements, the mechanism should be such that there is confidence that all notifications are received; in that, a confirmation and/or reconciliation process should be undertaken.

iv. Correct data entry, including the appropriate use of terminologies, should be verified by quality assurance auditing, either systematically or by regular random evaluation. Data entry staff should be instructed in the use of the MedDRA terminologies and relevant reporting platforms.

v. Data received from the primary source should be treated in an unbiased and unfiltered way and inferences as well as imputations should be avoided during data entry or electronic transmission. The reports should include the verbatim text as used by the primary source or an accurate translation of it.

vi. Electronic data storage should allow traceability (audit trail) of all data entered or modified, including dates and sources of received data, as well as dates and destinations of transmitted data.

vii. A procedure should be in place to account for identification and management of duplicate cases at data entry and during the generation of aggregated reports.

6.4.19. **Quality management**

i. The MAHs should have a quality management system in place to ensure compliance with the necessary quality standards at every stage of case documentation, such as data collection, data transfer, data management, data coding, case validation, case evaluation, case follow-up, ICSR reporting and case archiving. Conformity of stored data with initial and follow-up reports should be verified by quality control procedures, which permit validation against the original data or images thereof. In this respect, the source data (e.g., letters, emails, records of telephone calls that include details of an event) or an image of the source data should be easily accessible.

ii. Clear written standard operating procedures should guarantee that the roles and responsibilities and the required tasks are clear to all parties involved and that there is provision for proper control and, when needed, change of system. This is equally applicable to activities that are contracted out to third parties, whose

procedures should be reviewed to verify that they are adequate and compliant with applicable requirements.

iii. Personnel directly performing safety monitoring activities should be appropriately trained in applicable safety monitoring legislation and guidelines in addition to specific training in report processing activities for which they are responsible and/or undertake. Other personnel who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control) should be trained in adverse event collection and reporting in accordance with internal policies and procedures. (Refer to *Guidelines on QPPV and Safety Monitoring regulations*)

7. PERIODIC SAFETY UPDATE REPORTS /PERIODIC BENEFIT RISK EVALUATION REPORTS

7.1. The scope, objectives, format and content of the PSUR/PBRER

7.1.1. PSURs/PBRERs are applicable to all medicines and allied substances granted marketing authorisation in Zambia.

7.1.2. A Periodic Benefit Risk Evaluation Report (PBRER) previously referred to as PSUR is a comprehensive, concise, and critical analysis of new or emerging information on the risks and benefits of a medicine compiled by the MAH. These ongoing appraisals aid both the MAH and the regulator in maintaining confidence in the benefit-risk balance of the medicine based on the regulatory options currently imposed (such as approved indications, warnings, labelling) and those yet available (e.g., limiting the indications, expanding warnings and precautions, creating contraindications, rescheduling, relabeling or restricting use to a subset of the population).

7.1.3. The Authority uses the information in PSUR/PBRERs to determine if there are new risks identified for a medicine or whether the balance of benefits and risks of a medicine or allied substance has changed. It can then

decide if further investigations need to be carried out or can take action to protect the public from the risks identified, such as updating the information provided for healthcare professionals and patients.

7.1.4. The dates of submission according to the specified frequency shall be calculated from the date of the authorisation. Periodic Safety Update/PBRER reports shall be submitted to the Authority upon request within 15 days or in accordance with the following:

i. For new chemical entities and biologicals that have not yet been placed on the market, at least every 6 months following authorisation;

ii. Notwithstanding (i), Where a medicine or allied substance has been on the market, the following periodicity shall apply:

a) New chemical entities (NCEs) and biologicals at least every six (6) months for the first two (2) years, annually for the following three (3) years, and every five (5) years, at the time of renewal of license.

b) For all other products the most recent PSURs/PBRERs should be submitted at the time of renewal of Marketing Authorisation of the product.

c) Notwithstanding the above, the Authority may also request Ad hoc PSUR/ PBRERs, i.e., reports

outside the specified reporting requirements when there are new risks, when risks have changed, when efficacy has changed, or when there are changes to the benefit-risk profile of the registered product. A period of not more than thirty days shall be required for submission of the report.

d) For listed medicines and allied substances (emergency use authorisation), the MAH shall submit a PSUR/PBRER every six (6) months for the listing period.

iii. Each MAH should be responsible for submitting PSUR/PBRERs for its own products to the Authority according to the following timelines:

a) Within 70 calendar days of the data lock point (day 0) for PSUR/PBRERs/ covering intervals up to 12 months (including intervals of exactly 12 months); and

b) Within 90 calendar days of the data lock point (day 0) for PSUR/PBRERs covering intervals more than 12 months;

7.1.5. The obligations imposed in respect of PSUR/PBRERs should be proportionate to the risks posed by the medicine or allied substance. PSUR/PBRER reporting

should therefore be linked to the risk management systems of a medicine or allied substance.

7.2. Structures and processes Objectives

7.2.1. The main objective of a PSUR/PBRER is to present a comprehensive, concise and critical analysis of the benefit-risk balance of the medicine or allied substance considering new or emerging information in the context of cumulative information on risks and benefits. The PSUR/PBRER is therefore a tool for post-authorisation evaluation at defined time points in the lifecycle of a product.

7.2.2. For the purposes of lifecycle benefit-risk management, it is necessary to continue evaluating the risks and benefits of a medicine or allied substance in everyday medicinal practice and long-term use in the post-authorisation phase. This may extend to evaluation of populations and endpoints that could not be investigated in the pre-authorisation clinical trial. A different benefit-risk balance may emerge as safety monitoring reveals further information about safety. The MAH should therefore re-evaluate the benefit-risk balance of its own medicines and allied substances in populations exposed. This structured evaluation should be undertaken in the context of ongoing safety

monitoring and risk management to facilitate optimisation of the benefit-risk balance through effective risk minimisation.

7.2.3. Urgent safety information should be reported through the appropriate mechanism. A PSUR/PBRER is not intended, in the first instance, for notification of significant new safety or efficacy information or to provide how new safety issues are detected. It is acknowledged that the review of the data in the PSUR/PBRER may lead to new safety issues being identified.

7.3. Principles for the evaluation of the benefit-risk balance within PSUR/PBRERs and scope of the information to be included

7.3.1. **Principles**

i. Benefit-risk evaluation should be carried out throughout the lifecycle of the medicine or allied substance to promote and protect public health and to enhance patient safety through effective risk minimisation.

ii. After a Marketing Authorisation is granted, it is necessary to continue evaluating the benefits and risks of medicines and allied substances in actual use and/or

long-term use, to confirm that the benefit-risk balance remains favourable.

iii. The analysis of the benefit-risk balance should incorporate an evaluation of the safety, efficacy and effectiveness information that becomes available, with reasonable and appropriate effort, during the reporting interval for the medicine or allied substance in the context of what was known previously.

iv. The risk evaluation should be based on all uses of the medicine or allied substances. The scope includes evaluation of safety in real medicinal practice including use in unauthorised indications and use which is not in line with the product information. If use of the medicine or allied substance is identified where there are critical gaps in knowledge for specific safety issues or populations, such use should be reported in the PSUR/PBRER (e.g. use in paediatric population or in pregnant women). Sources of information on use outside authorisation may include drug utilisation data, information from spontaneous reports and publications in the literature.

7.3.2. **Scope**

i. The scope of the benefit-risk information should include both clinical trial and real-world data in authorised indications.

ii. The integrated benefit-risk evaluation should be performed for all authorised indications and should incorporate the evaluation of risks in all uses of the medicine or allied substance (including use in unauthorised indications).

iii. The evaluation should involve:

a) Critically examining the information which has emerged during the reporting interval to determine whether it has generated new signals, led to the identification of new potential or identified risks or contributed to knowledge of previously identified risks.

b) Critically summarising relevant new safety, efficacy and effectiveness information that could have an impact on the benefit-risk balance of the medicine or allied substance. (Including safety, efficacy and effectiveness information generated in Zambia.)

c) Conducting an integrated benefit-risk analysis for all authorised indications based on the cumulative information available since the development international birth date (DIBD), the date of first authorisation for the conduct of an interventional clinical trial in any country. For cases where the

DIBD is unknown or the MAH does not have access to data from the clinical development period, the earliest possible applicable date should be used as a starting point for the inclusion and evaluation of cumulative information.

d) Summarising any risk minimisation actions that may have been taken or implemented during the reporting interval, as well as risk minimisation actions that are planned to be implemented.

e) Outlining plans for signal or risk evaluations including timelines and/or proposals for additional safety monitoring activities.

f) Principles for the preparation of PSUR/PBRERs

iv. Unless otherwise specified by the Authority, the MAH should prepare a single PSUR/PBRER for all its medicines and allied substances containing the same active substance with information covering all the authorised indications, route of administration, dosage forms and dosing regiments, irrespective of whether authorised under different names and through separate procedures. Where relevant, data relating to a particular indication, dosage form, route of administration or dosing regimen should be presented in a separate section of the PSUR/PBRER, and any safety concerns

should be addressed accordingly. There might be exceptional scenarios where the preparation of separate PSUR/PBRERs might be appropriate, for instance, in the event of different formulations for entirely different indications. In this case, agreement should be obtained from the Authority preferably at the time of authorisation.

v. Case narratives should be provided in the relevant risk evaluation section of the PSUR/PBRER were integral to the scientific analysis of a signal or safety concern. In this context, the term "case narratives" refers to clinical evaluations of individual cases rather than the CIOMS narratives.

vi. When data received at the MAH from a partner might contribute meaningfully to the safety, benefit and/or benefit-risk analyses and influence the reporting MAH's product information, these data should be included and discussed in the PSUR/PBRER.

vii. The format and table of contents of all PSUR/PBRERs should be as described in sections 7.3.4 and 7.3.5. Each report should include interval as well as cumulative data.

7.3.3. **Reference information**

i. Risk minimisation activities evaluated in the PSUR/PBRER include updates to the product information.

ii. The reference product information for the PSUR/PBRER should include "core safety" and "authorised indications" components. To facilitate the assessment of benefit and benefit-risk balance by indication in the evaluation sections of the PSUR/PBRER, the reference product information document should list all authorised indications.

iii. The basis for the benefit evaluation should be the important baseline efficacy and effectiveness information summarised in the PSUR/PBRER section "Important baseline efficacy and effectiveness information".

iv. Information related to a specific indication, formulation or route of administration should be clearly identified in the reference product information.

v. The following possible options can be considered by the MAHs when selecting the most appropriate reference product information for a PSUR/PBRER:

a. Company core data sheet (CCDS)

(i) It is common practice for MAHs to prepare their own company core data sheet which covers data relating to safety, indications, dosing, pharmacology, and other information concerning the product. The core safety information contained within the CCDS is referred to as the company core safety information (CCSI). A practical option for the purpose of the PSUR/PBRER is for each MAH to use the CCDS in effect at the end of the reporting interval, as reference product information for both the risk sections of the PSUR/PBRER as well as the main authorised indications for which benefit is evaluated.

(ii) When the CCDS does not contain information on authorised indications, the MAH should clearly specify which document is used as reference information for the authorised indications in the PSUR/PBRER.

b. Other options for the reference product information

(i) When no CCDS or CCSI exist for a product (e.g. established/generic products on the market for many years), the MAH should clearly specify the reference information being used.

(ii) Where the reference information for the authorised indications is a separate document to the reference safety information (the core safety information contained within the reference product information), the version in effect at the end of the reporting interval should be included as an appendix to the PSUR/PBRER.

vi. The MAH should continuously evaluate whether any revision of the reference product information/reference safety information is needed whenever new safety information is obtained during the reporting interval and ensure that significant changes made over the interval are described in PSUR/PBRER "Changes to the reference safety information" and where relevant, discussed in PSUR/PBRER "Signal and risk evaluation". These changes may include:

a) A change to contraindications, warnings/precautions sections;
b) Addition to adverse reactions and interactions;
c) Addition of important new information on use in overdose; and
d) Removal of an indication or other restrictions for safety or lack
of efficacy reasons.

vii. The MAH should provide a clean copy of all versions of the reference product information in effect at the end of the reporting interval (e.g. different formulations included in the same PSUR/PBRER) as an appendix to the PSUR/PBRER. The reference product information should be dated and version controlled.

viii. Where new information on safety that could warrant changes to the authorised product information (e.g. new adverse drug reaction, warning or contraindication) has been added to the reference safety information during the period from the data lock point to the submission of the PSUR/PBRER, this information should be included in the PSUR/PBRER ("Late-breaking information").

7.3.4. Format and contents of the PSUR/PBRER

i. The PSUR/PBRER should be based on all available data including those generated from within Zambia and should focus on new information which has emerged since the data lock point of the last PSUR/PBRER. Cumulative information should be considered when performing the overall safety evaluation and integrated benefit- risk assessment.

ii. Because clinical development of a medicine or allied substance frequently continues following Marketing Authorisation, relevant information from post-authorisation studies or clinical trials in unauthorised indications or populations should also be included in the PSUR/PBRER. Similarly, as knowledge of the safety of a medicine or allied substance may be derived from evaluation of other data associated with off-label use, such knowledge should be reflected in the risk evaluation where relevant and appropriate.

iii. The PSUR/PBRER should provide summaries of data relevant to the benefits and risks of the medicine or allied substance, including results of all studies with consideration of their potential impact on Marketing Authorisation.

iv. Examples of sources of efficacy, effectiveness and safety information that may be used in the preparation of PSUR/PBRERs include the following:

a) Non-clinical studies;
b) Spontaneous reports (e.g. on the MAH's safety database);
c) Active surveillance systems (e.g. sentinel sites);
d) Investigations of product quality;
e) Product usage data and drug utilisation information;
f) Clinical trials, including research in unauthorised indications or populations;
g) Observational studies, including registries;
h) Patient support programs;
i) Systematic reviews and meta-analysis;
j) MAHs sponsored websites;
k) Published scientific literature or reports from abstracts, including information presented at scientific meetings;
l) Unpublished manuscripts;
m) Licensing partners, other sponsors or academic institutions and research networks;
n) Competent authorities (worldwide).

v. The above list is not intended to be all inclusive, and additional data sources may be used by the MAH to

present safety, efficacy and effectiveness information in the PSUR/PBRER and to evaluate the benefit-risk balance, as appropriate to the product and its known and emerging important benefits and risks. A list of the sources of information used to prepare the PSUR/PBRER can be provided as an appendix to the PSUR/PBRER.

vi. The PSUR/PBRER should be prepared following the format in section 7.3.4.

vii. Sources of information include data regarding the active substance(s) included in the medicine or allied substance, or the medicine or allied substance that the MAH may reasonably be expected to have access to and that are relevant to the evaluation of the safety, and/or benefit-risk balance. It is therefore recognised that while the same format should be followed for all products, the extent of the information provided may vary where justified according to what is accessible to the MAH. For example, for MAH sponsored clinical trials, there should be access to patient level data while for a clinical trial not sponsored by the MAH, only the published report may be accessible.

viii. The level of detail provided in certain sections of the PSUR/PBRER should depend on known or emerging important information on the medicine or allied

substance's benefits and risks. This approach is applicable to those sections of the PSUR/PBRER in which there is evaluation of information about safety, efficacy, effectiveness, safety signals and benefit-risk balance.

7.3.5. When preparing the PSUR/PBRER, the ICH-E2C(R2) guideline (see Annex IV ICH-E2C(R2)) on Periodic Benefit-Risk Evaluation Report (PBRER) should also be applied. Guidance on the titles, order and content of the PSUR/PBRER sections is provided below. When no relevant information is available for any of the sections, this should be stated.

Part I: Title page including signature

Part II: Executive Summary

Part III: Table of Contents

1. Introduction
2. Worldwide Marketing Authorisation status
3. Actions taken in the reporting interval for safety reasons
4. Changes to reference safety information
5. Estimated exposure and use patterns

5.1. Cumulative subject exposure in clinical trials

5.2. Cumulative and interval patient exposure from marketing experience

6. Data in summary tabulations

6.1. Reference information

6.2. Cumulative summary tabulations of serious adverse events from clinical trials

6.3. Cumulative and interval summary tabulations from post-marketing data sources

7. Summaries of significant findings from clinical trials during the reporting interval

7.1. Completed clinical trials

7.2. Ongoing clinical trials

7.3. Long-term follow-up

7.4. Other therapeutic use of medicine or allied substance

7.5. New safety data related to fixed combination therapies

8. Findings from non-interventional studies

9. Information from other clinical trials and sources

9.1. Other clinical trials

9.2. Medication errors

10. Non-clinical Data

11. Literature

12. Other periodic reports

13. Lack of efficacy in controlled clinical trials

14. Late-breaking information

15. Overview of signals: new, ongoing or closed

16. Signal and risk evaluation

16.1. Summaries of safety concerns

16.2. Signal evaluation

16.3. Evaluation of risks and new information

16.4. Characterisation of risks

16.5. Effectiveness of risk minimisation (if applicable)

17. Benefit evaluation

17.1. Important baseline efficacy and effectiveness information

17.2. Newly identified information on efficacy and effectiveness

17.3. Characterisation of benefits

18. Integrated benefit-risk analysis for authorised indications

18.1. Benefit-risk context – Medicinal need and important alternatives

18.2. Benefit-risk analysis evaluation

19. Conclusions and actions

20. Appendices to the PSUR/PBRER

Part I Title page

The title page should include the following:

i. Name of the medicine or allied substance(s) and substance;
ii. International birth date (IBD) (the date of the first Marketing Authorisation for any product containing the active substance granted to any company in any country in the world);
iii. Date of first registration in Zambia
iv. Reporting interval;
v. Date of the report;
vi. MAH details;
vii. Statement of confidentiality of the information included in the PSUR/PBRER.
viii. Signature of QPPV in Zambia

Part II Executive summary

An executive summary should be placed immediately after the title page and before the table of contents. The purpose of the executive summary is to provide a concise summary of the content and the most important information in the PSUR/PBRER and should contain the following information:

1. Introduction and reporting interval;

2. Medicine or allied substance(s), therapeutic class(es), mechanism(s) of action, indication(s), pharmaceutical formulation(s), dose(s) and route(s) of administration;
3. Estimated cumulative clinical trials exposure;
4. Estimated interval and cumulative exposure from marketing experience;
5. Number of countries in which the medicine or allied substance is authorised;
6. Summary of the overall benefit-risk analysis evaluation (based on "Benefit-risk analysis evaluation" of the PSUR/PBRER);
7. Actions taken and proposed for safety reasons, (e.g. significant changes to the reference product information, or other risk minimisation activities);
8. Conclusions.

Part III Table of contents

The executive summary should be followed by the table of contents.

1. Introduction

The MAH should briefly introduce the product(s) so that the PSUR/PBRER "stands alone" but it is also placed in perspective relative to previous PSUR/PBRERs and

circumstances. The introduction should contain the following information:

a. International birth date (IBD), and reporting interval;
b. Medicine or allied substance(s), therapeutic class(es), mechanism(s) of action, authorised indication(s), pharmaceutical form(s), dose(s) and route(s) of administration;
c. Brief description of the population(s) being treated and studied;

2. Worldwide Marketing Authorisation status

This section of the PSUR/PBRER should contain a brief narrative overview including:

a. Date of the first authorisation worldwide,
b. Indications(s),
c. Authorised dose(s), and where authorised.

3. Actions taken in the reporting interval for safety reasons

This section of the PSUR/PBRER should include a description of significant actions related to safety that have been taken worldwide during the reporting interval, related to either investigational uses or marketing experience by the Marketing Authorisation holder, sponsors of clinical trial(s), data

monitoring committees, ethics committees or the Authority that had either:

a. A significant influence on the benefit-risk balance of the authorised medicine or allied substance; and/or
b. An impact on the conduct of a specific clinical trial(s) or on the overall clinical development programme.

If known, the reason for each action should be provided and any additional relevant information should be included as appropriate. Relevant updates to previous actions should also be summarised in this section.

Examples of significant actions taken for safety reasons include:

a. Actions related to investigational uses:
    i. Refusal to authorise a clinical trial for ethical or safety reasons;
    ii. Partial or complete clinical trial suspension or early termination of an ongoing clinical trial because of safety findings or lack of efficacy;
    iii. Recall of investigational drug or comparator;
    iv. Failure to obtain Marketing Authorisation for a tested indication including voluntary withdrawal of a Marketing Authorisation application;
    v. Risk management activities, including:

- Protocol modifications due to safety or efficacy concerns (e.g. dosage changes, changes in study inclusion/exclusion criteria, intensification of subject monitoring, limitation in trial duration);

- Restrictions in study population or indications;

- Changes to the informed consent document relating to safety concerns;

- Formulation changes;

- Addition by regulators of a special safety-related reporting requirement;

- Issuance of communication to investigators or healthcare professionals; and

- Plans for new studies to address safety concerns.

b. Actions related to marketing experience:
   i. Failure to obtain or apply for a Marketing Authorisation renewal;
   ii. Withdrawal or suspension of a Marketing Authorisation;
   iii. Actions taken due to product defects and quality issues;
   iv. Suspension of supply by the MAH;

v. Risk management activities including:

- Significant restrictions on distribution or introduction of other risk minimisation measures;

- Significant safety-related changes in labelling documents including restrictions on use or population treated;

- Communications with health care professionals; and

- New post-marketing study requirement(s) imposed by the Authority.

4. Changes to reference safety information

This PSUR/PBRER section should list any significant changes made to the reference safety information within the reporting interval. Such changes might include information relating to contraindications, warnings, precautions, serious adverse drug reactions, interactions, important findings from ongoing or completed clinical trials and significant non-clinical findings (e.g. carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the PSUR/PBRER.

5. Estimated exposure and use patterns

i. PSUR/PBRERs should provide an accurate estimate of the population exposed to the medicine or allied substance, including all data relating to the volume of sales and volume of prescriptions. This estimate of exposure should be accompanied by a qualitative and quantitative analysis of actual use, which should indicate, where appropriate, how actual use differs from the indicated use based on all data available to the Marketing Authorisation holder, including the results of observational or drug utilisation studies.

ii. This PSUR/PBRER section should provide estimates of the size and nature of the population exposed to the medicine or allied substance including a brief description of the method(s) used to estimate the subject/patient exposure and the limitations of that method.

iii. Consistent methods for calculating subject/patient exposure should be used across PSUR/PBRERs for the same medicine or allied substance. If a change in the method is appropriate, both methods and calculations should be provided in the PSUR/PBRER introducing the change and any important difference between the results using the two methods should be highlighted.

5.1. Cumulative subject exposure in clinical trials

This section of the PSUR/PBRER should contain the following information on the patients studied in clinical trials sponsored by the Marketing Authorisation holder, if applicable presented in tabular formats:

a. Cumulative numbers of subjects from ongoing and completed clinical trials exposed to the investigational medicine or allied substance, placebo, and/or active comparator(s) since the Development International Birth Date (DIBD). It is recognised that for "old products", detailed data might not be available;
b. More detailed cumulative subject exposure in clinical trials should be presented if available (e.g. sub-grouped by age, sex, and racial/ethnic group for the entire development programme);
c. Important differences among trials in dose, routes of administration, or patient populations can be noted in the tables, if applicable, or separate tables can be considered;
d. If clinical trials have been or are being performed in special populations (e.g. pregnant women; patients with renal, hepatic, or cardiac impairment; or patients with relevant genetic polymorphisms), exposure data should be provided as appropriate;

e. When there are substantial differences in time of exposure between subjects randomised to the investigational medicine or allied substance or comparator(s), or disparities in length of exposure between clinical trials, it can be useful to express exposure in subject-time (subject-days, -months, or -years);

f. Investigational drug exposure in healthy volunteers might be less relevant to the overall safety profile, depending on the type of adverse reaction, particularly when subjects are exposed to a single dose. Such data can be presented separately with an explanation as appropriate;

g. If the serious adverse events from clinical trials are presented by indication in the summary tabulations, the patient exposure should also be presented by indication, where available;

h. For individual trials of particular importance, demographic characteristics should be provided separately.

Provide examples in a table for the estimated exposure in clinical trials.

5.2. Cumulative and interval patient exposure from marketing experience

Separate estimates should be provided for cumulative exposure (since the IBD), when possible, and interval exposure (since the data lock point of the previous PSUR/PBRER). Although it is recognised that it is often difficult to obtain and validate exposure data, the number of patients exposed should be provided whenever possible, along with the method(s) used to determine the estimate. Justification should be provided if it is not possible to estimate the number of patients exposed. In this case, alternative estimates of exposure, if available, should be presented along with the method(s) used to derive them. Examples of alternative measures of exposure include patient-days of exposure and number of prescriptions. Only if such measures are not available, measures of drug sales, such as tonnage or dosage units, may be used. The concept of a defined daily dose may also be used to arrive at patient exposure estimates.

The data should be presented in the following categories:

a. Post-authorisation (non-clinical trial) exposure:

An overall estimation of patient exposure should be provided. In addition, the data should be routinely presented by sex, age, indication, dose, formulation and region, where applicable.

Depending upon the product, other variables may be relevant, such as number of vaccination courses, route(s) of administration, and duration of treatment. When there are patterns of reports indicating a safety signal, exposure data within relevant subgroups should be presented, if possible.

b. Post-authorisation uses in special populations:

Where post-authorisation use has occurred in special populations, available information regarding cumulative patient numbers exposed and the method of calculation should be provided. Sources of such data may include for instance non-interventional studies designed to obtain this information, including registries. Other sources of information may include data collection outside a study environment including information collected through spontaneous reporting systems (e.g. information on reports of pregnancy exposure without an associated adverse event may be summarised in this section). Populations to be considered for discussion include, but might not be limited to:

- Paediatric population;
- Elderly population;
- Pregnant or lactating women;
- Patients with hepatic and/or renal impairment;

- Patients with other relevant co-morbidity;

- Patients with disease severity different from that studied in clinical trials;

- Sub-populations carrying relevant genetic polymorphism(s);

- Populations with specific racial and/or ethnic origins.

c. Other post-authorisation use:

i. If the MAH becomes aware of a pattern of use of the medicine or allied substance, which may be regional, considered relevant for the interpretation of safety data, provide a brief description thereof. Examples of such patterns of use may include evidence of overdose, abuse, misuse and use beyond the recommendation(s) in reference product information (e.g. an anti-epileptic drug used for neuropathic pain and/or prophylaxis of migraine headaches). Where relevant to the evaluation of safety and/or benefit-risk, information reported on patterns of use without reference to adverse reactions should be summarised in this section as applicable. Such information may be received via spontaneous reporting systems, medicinal information queries, customer complaints, screening of digital media or via other information sources available to the MAH. If

quantitative information on use is available; it should be provided.

ii. If known, the MAH may briefly comment on whether other use beyond the recommendation(s) in the reference product information may be linked to clinical guidelines, clinical trial evidence, or an absence of authorised alternative treatments. For purposes of identifying patterns of use outside the terms of the reference product information, the MAH should use the appropriate sections of the reference product information that was in effect at the end of the reporting interval of the PSUR/PBRER (e.g. authorised indication, route of administration, contraindications).

iii. Signals or risks identified from any data or information source should be presented and evaluated in the relevant sections of the PSUR/PBRER.

Insert tables for the estimated exposure from marketing experience.

6. Data in summary tabulations

The objective of this PSUR/PBRER section is to present safety data through summary tabulations of serious adverse events from clinical trials, spontaneous serious and non-serious reactions from marketing experience (including reports from

healthcare professionals, consumers, scientific literature, the competent authorities (worldwide)) and serious reactions from non-interventional studies and other non- interventional solicited source. At the discretion of the MAH graphical displays can be used to illustrate specific aspects of the data when useful to enhance understanding.

When the Medicinal Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse event/reaction terms, the preferred term (PT) level and system organ class (SOC) should be presented in the summary tabulations.

The seriousness of the adverse events/reactions in the summary tabulations should correspond to the seriousness assigned to events/reactions included in the ICSRs using the criteria established in ICH-E2A9. When serious and non-serious events/reactions are included in the same ICSR, the individual seriousness per reaction should be reflected in the summary tabulations. Seriousness should not be changed specifically for the preparation of the PSUR/PBRERs.

6.1. Reference information

This section of the PSUR/PBRER should specify the version(s) of the coding dictionary used for presentation of adverse events/reactions.

6.2. Cumulative summary tabulations of serious adverse events from clinical trials

This PSUR/PBRER section should provide background for the appendix that provides a cumulative summary tabulation of serious adverse events reported in the MAH's clinical trials, from the DIBD to the data lock point of the current PSUR/PBRER. The MAH should explain any omission of data (e.g. clinical trial data might not be available for products marketed for many years). The tabulation(s) should be organised by MedDRA SOC (listed in the internationally agreed order), for the investigational drug, as well as for the comparator arm(s) (active comparators, placebo) used in the clinical development programme. Data can be integrated across the programme. Alternatively, when useful and feasible, data can be presented by trial, indication, route of administration or other variables.

This section should not serve to provide analyses or conclusions based on serious adverse events.

The following points should be considered:

a. Causality assessment is generally useful for the evaluation of individual rare adverse drug reactions. Individual case causality assessment has less value in the analysis of aggregate data, where group comparisons of rates are possible. Therefore, the summary tabulations should include all serious adverse events and not just serious adverse reactions for the investigational drug, comparators and placebo. It may be useful to give rates by dose.

b. In general, the tabulation(s) of serious adverse events from clinical trials should include only those terms that were used in defining the case as serious and non-serious events should be included in the study reports.

c. The tabulations should include blinded and unblind clinical trial data. Unblinded serious adverse events might originate from completed trials and individual cases that have been unblinded for safety-related reasons (e.g. expedited reporting), if applicable. Sponsors of clinical trials and MAHs should not unblind data for the specific purpose of preparing the PSUR/PBRER.

d. Certain adverse events can be excluded from the clinical trials summary tabulations, but such exclusions

should be explained in the report. For example, adverse events that have been defined in the protocol as "exempt" from special collection and entry into the safety database because they are anticipated in the patient population, and those that represent study endpoints, can be excluded (e.g. deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials).

Provide tables of the summary of serious adverse events from clinical trials.

6.3. Cumulative and interval summary tabulations from post-marketing data sources

This section of the PSUR/PBRER should provide background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the IBD to the data lock point of the current PSUR/PBRER. These adverse reactions are derived from spontaneous ICSRs including reports from healthcare professionals, consumers, scientific literature, competent authorities (worldwide) and from solicited non-interventional ICSRs including those from non-interventional studies. Serious and non-serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other non-interventional

solicited sources should be presented in a single table, with interval and cumulative data presented side by side. The table should be organised by MedDRA SOC (listed in the internationally agreed order).

For special issues or concerns, additional tabulations of adverse reactions can be presented by indication, route of administration, or other variables.

As described in ICH-E2D11 guideline, for marketed medicines and allied substances, spontaneously reported adverse events usually imply at least a suspicion of causality by the reporter and should be suspected adverse reactions of regulatory reporting purposes.

Analysis or conclusions based on the summary tabulations should not be provided in this PSUR/PBRER section.

Provide summary tables of adverse drug reactions from post-marketing data sources.

7. Summaries of significant findings from clinical trials during the reporting interval

This PSUR/PBRER section should provide a summary of the clinically important emerging efficacy and safety findings obtained from the MAH's sponsored clinical trials during the reporting interval, from the sources specified in the sections

listed below. When possible and relevant, data categorised by sex and age (particularly paediatrics versus adults), indication, dose, and region should be presented.

Signals arising from clinical trial sources should be tabulated in PSUR/PBRER section 15 ("Overview on signals: new, ongoing or closed"). Evaluation of the signals, whether categorised as refuted signals or either potential or identified risk, that were closed during the reporting interval should be presented in PSUR/PBRER section, "Signal evaluation". New information in relation to any previously known potential or identified risks and not considered to constitute a newly identified signal should be evaluated and characterised in PSUR/PBRER section, "Evaluation of risks and new information" and section, "Characterisation of risks", respectively.

Findings from clinical trials not sponsored by the MAH should be described in the relevant sections of the PSUR/PBRER.

When relevant to the benefit-risk evaluation, information on lack of efficacy from clinical trials for treatments of non-life-threatening diseases in authorised indications should also be summarised in this section. Information on lack of efficacy from clinical trials with products intended to treat or prevent serious or life-threatening illness should be summarised in "Lack of efficacy in controlled clinical trials".

Information from other clinical trials/study sources should be included in the PSUR/PBRER "other clinical trials".

In addition, the MAH should include an appendix listing the sponsored post-authorisation interventional trials with the primary aim of identifying, characterising, or quantifying a safety hazard or confirming the safety profile of the medicines and allied substances that were completed or ongoing during the reporting interval. The listing should include the following information for each trial:

a. Study ID (e.g. protocol number or another identifier);
b. Study title (abbreviated study title, if applicable);
c. Study type (e.g. randomised clinical trial, cohort study, case- control study);
d. Population studied, including country and other relevant population descriptors (e.g. paediatric population or trial subjects with impaired renal function);
e. Study starts (as defined by the Marketing Authorisation holder) and projected completion dates;
f. Status: ongoing (clinical trial has begun) or completed (clinical study report is finalised).

7.1. Completed clinical trials

This section of the PSUR/PBRER should provide a summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed during the reporting interval. This information can be presented in narrative format or as a synopsis. It could include information that supports or refutes previously identified safety concerns as well as evidence of new safety signals.

7.2. Ongoing clinical trials

If the MAH is aware of clinically important information that has arisen from ongoing clinical trials (e.g. learned through interim safety analyses or because of unblinding of subjects with adverse events), this section should briefly summarise the concern(s). It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

7.3. Long term follow-up

Where applicable, this section should provide information from long- term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products (e.g. gene therapy, cell therapy products and tissue engineered products)

7.4. Other therapeutic use of medicine or allied substance

This section of the PSUR/PBRER should include clinically important safety information from other programmes conducted by the MAH that follow a specific protocol, with solicited reporting as per ICH-E2D13 (e.g. expanded access programmes, compassionate use programmes, particular patient use, and other organised data collection).

7.5. New safety data related to fixed combination therapies

Unless otherwise specified by the Authority, the following options can be used to present data from combination therapies:

a. If the active substance that is the subject of the PSUR/PBRERs is also authorised or under development as a component of a fixed combination product or a multi-drug regimen, this section should summarise important safety findings from use of combination therapy.
b. If the product itself is a fixed combination product, this PSUR/PBRER section should summarise important safety information arising from the individual components whether authorised or under development.

The information specific to the combination can be incorporated into a separate section(s) of the PSUR/PBRER for one or all the individual components of the combination.

8. Findings from non-interventional studies

This section should also summarise relevant safety information or information with potential impact in the benefit-risk assessment from MAH-sponsored non-interventional studies that became available during the reporting interval (e.g. observational studies, epidemiological studies, registries, and active surveillance programmes). This should include relevant information from drug utilisation studies when relevant to multiple regions.

The MAH should include an appendix listing

MAH-sponsored non-interventional studies conducted with the primary aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicine or allied substance, or of measuring the effectiveness of risk management measures which were completed or ongoing during the reporting interval. for the information that should be included in the listing).

Final study reports completed during the reporting interval for the studies mentioned in the paragraph above should also be included in the regional appendix of the PSUR/PBRER.

Summary information based on aggregate evaluation of data generated from patient support programs may be included in this section when not presented elsewhere in the

PSUR/PBRER. As for other information sources, the MAH should present signals or risks identified from such information in the relevant sections of the PSUR/PBRER.

9. Information from other clinical trials and sources

9.1. Other clinical trials

This PSUR/PBRER section should summarise information relevant to the benefit-risk assessment of the medicine or allied substance from other clinical trial/study sources which are accessible by the MAH during the reporting interval (e.g. results from pool analysis or meta-analysis of randomised clinical trials, safety information provided by co-development partners or from investigator-initiated trials).

9.2. Medication errors

This section should summarise relevant information on patterns of medication errors and potential medication errors, even when not associated with adverse outcomes. A potential medication error is the recognition of circumstances that could lead to a medication error and may or may not involve a patient. Such information may be relevant to the interpretation of safety data or the overall benefit-risk evaluation of the medicine or allied substance. A medication error may arise at any stage in the medication use process and may involve patients, consumers, or healthcare professionals.

10. Non-clinical data

This PSUR/PBRER section should summarise major safety findings from non-clinical in vivo and in vitro studies (e.g. carcinogenicity, reproduction or immunotoxicity studies) ongoing or completed during the reporting interval. Results from studies designated to address specific safety concerns should be included in the PSUR/PBRER, regardless of the outcome. Implications of these findings should be discussed in the relevant evaluation sections of the PSUR/PBRER.

11. Literature

This PSUR/PBRER section should include a summary of new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts that the MAH became aware of during the reporting interval, when relevant to the medicine or allied substance.

Literature searches for PSUR/PBRERs should be wider than those for individual adverse reaction cases as they should also include studies reporting safety outcomes in groups of subjects and other products containing the same active substance.

The special types of safety information that should be included, but which may not be found by a search constructed specifically to identify individual cases, include:

a. Pregnancy outcomes (including termination) with no adverse outcomes;
b. Use in paediatric populations;
c. Compassionate supply, named patient use;
d. Lack of efficacy;
e. Asymptomatic overdose, abuse or misuse;
f. Medication error where no adverse events occurred;
g. Important non-clinical safety results.

If relevant and applicable, information on other active substances of the same class should be considered. The reference should be provided in the style of the Vancouver Convention.

12. Other periodic reports

This PSUR/PBRER section will only apply in certain circumstances concerning fixed combination products or products with multiple indications and/or formulations where multiple PSUR/PBRERs are prepared in agreement with the Authority. In general, the MAH should prepare a single PSUR/PBRER for a single active substance (unless otherwise specified by the Authority); however, if multiple PSUR/PBRERs are prepared for a single medicine or allied substance, this section should also summarise significant findings from other PSUR/PBRERs if they are not presented elsewhere within the report.

When available, based on the contractual agreements, the MAH should summarise significant findings from periodic reports provided during the reporting interval by other parties (e.g. sponsors, other MAHs or other contractual partners).

13. Lack of efficacy in controlled clinical trials

This section should summarise data from clinical trials indicating lack of efficacy, or lack of efficacy relative to established therapy(ies), for products intended to treat or prevent serious or life-threatening illnesses (e.g. excess cardiovascular adverse events in a trial of a new anti-platelet medicine for acute coronary syndromes) that could reflect a significant risk to the treated population.

14. Late-breaking information

The MAH should summarise in this PSUR/PBRER section the potentially important safety, efficacy and effectiveness findings that arise after the data lock point but during the period of preparation of the PSUR/PBRER. Examples include clinically significant new publications, important follow-up data, clinically relevant toxicological findings and any action that the Marketing Authorisation holder, a data monitoring committee, or any competent Authority (worldwide) has taken for safety reasons. New individual case reports should not be routinely included unless they are considered to constitute an

important index case (i.e. the first instance of an important event) or an important safety signal or where they may add information to the evaluation of safety concerns already presented in the PSUR/PBRER (e.g. a well-documented case of aplastic anaemia in a medicine or allied substance known to be associated with adverse effects on the bone marrow in the absence of possible alternative causes).

Any significant change proposed to the reference product information (e.g. new adverse reaction, warning or contraindication) which has occurred during this period, should also be included in this section of the PSUR/PBRER.

The data presented in this section should also be considered in the evaluation of risks and new information.

15. Overview of signals: new, ongoing, or closed

The purpose of this section is to provide a high-level overview of signals that were closed (i.e. evaluation was completed) during the reporting interval as well as ongoing signals that were undergoing evaluation at the end of the reporting interval. For the purposes of the PSUR/PBRER, a signal should be included once it has undergone the initial screening or clarification step, and a determination made to conduct further evaluation by the Marketing Authorisation holder. It should be noted that a safety signal is not synonymous with a statistic of

disproportionate reporting for a specific medicine or allied substance/event combination as a validation step is required. Signals may be qualitative (e.g., a pivotal individual case safety report, case series) or quantitative (e.g. a disproportionality score, findings of a clinical trial or epidemiological study). Signals may arise in the form of an information request or inquiry into a safety issue from a competent Authority (worldwide).

Decisions regarding the subsequent classification of these signals and the conclusions of the evaluation, involve medicinal judgement and scientific interpretation of available data, which is presented in section "Signal and risk evaluation" of the PSUR/PBRER.

A new signal refers to a signal that has been identified during the reporting interval. Where new clinically significant information on a previously closed signal becomes available during the reporting interval of the PSUR/PBRER, this would also be considered a new signal on the basis that a new aspect of a previously refuted signal or recognised risk warrants further action to verify. New signals may be classified as closed or ongoing, depending on the status of signal evaluation at the end of the reporting interval of the PSUR/PBRER.

Examples of new signals would therefore include new information or on a previously:

a. Close and refuted signal, which would result in the signal being re-opened.
b. Identified risk where the new information suggests a clinically significant difference in the severity or frequency of the risk (e.g. transient liver enzyme increases are identified risks and new information indicative of a more severe outcome such as hepatic failure is received, or neutropenia is an identified risk and a well-documented case report of agranulocytosis with no presence of possible alternative causes is received).
c. Identified risk for which a higher frequency or severity of the risk is newly found (e.g. in an indicated subpopulation).
d. Potential risk which, if confirmed, would warrant a new warning, precaution, a new contraindication or restriction in indication(s) or population or other risk minimisation activities.

Within this section or as an appendix the MAH should provide a tabulation of all signals ongoing or closed at the end of the reporting interval. This tabulation should include the following information:

a. A brief description of the signal;
b. Date when the MAH became aware of the signal;

c. Status of the signal at the end of the reporting interval (close or ongoing);
d. Date when the signal was closed, if applicable;
e. Source of the signal;
f. A summary of the key data;
g. Plans for further evaluation; and
h. Actions taken or planned.

Provide tables of signals.

The detailed signal assessments for closed signals are not to be included in this section but instead should be presented in "Signal evaluation" of the PSUR/PBRER.

Evaluation of new information in relation to any previously known identified and potential risks and not considered to constitute a new signal should be provided in "Evaluation of risks and new information".

When any competent Authority (worldwide) has requested that a specific topic (not considered a signal) be monitored and reported in a PSUR/PBRER, the MAH should summarise the result of the analysis in this section if it is negative. If the specific topic becomes a signal, it should be included in the signal tabulation and discussed ("Signal evaluation").

16. Signal and risk evaluation

The purpose of this section of the PSUR/PBRER is to provide:

a. A succinct summary of what is known about important identified and potential risks and missing information at the beginning of the reporting interval covered by the report.
b. An evaluation of all signals closed during the reporting interval
c. An evaluation of new information with respect to previously recognised identified and potential risks.
d. An updated characterisation of important potential and identified risks, where applicable.
e. A summary of the effectiveness of risk minimisation activities in any country or region which may have utility in other countries or regions.

The information on signals and risks should be mapped in a flow chart.

These evaluation sections should not summarise, or duplicate information presented in previous sections of the PSUR/PBRER but should rather provide interpretation and critical appraisal of the information, with a view towards characterising the profile of those risks assessed as important. In addition, as a general rule, it is not necessary to include

individual case narratives in the evaluation sections of the PSUR/PBRER but where integral to the scientific analysis of a signal or risk, a clinical evaluation of pivotal or illustrative cases (e.g. the first case of suspected agranulocytosis with an active substance belonging to a class known to be associated with this adverse reaction) should be provided.

16.1. Summary of safety concerns

The purpose of this section is to provide a summary of important safety concerns at the beginning of the reporting interval, against which new information and evaluations can be made. For products with an existing safety specification, this section can be either the same as or derived from the safety specification summary that is current at the start of the reporting interval of the PSUR/PBRER. It should provide the following safety information:

a. Important identified risks;
b. Important potential risks; and
c. Missing information.

The following factors should be considered when determining the importance of each risk:

a. Medicinal seriousness of the risk, including the impact on individual patients;

b. Its frequency, predictability, preventability, and reversibility;
c. Potential impact on public health (frequency; size of treated population); and
d. Potential for avoidance of the use of a medicine or allied substance with a preventive benefit due to a disproportionate public perception of risk (e.g. vaccines).

For products without an existing safety specification, this section should provide information on the important identified and potential risks and missing information associated with use of the product, based on pre- and post-authorisation experience. Important identified and potential risks may include, for example:

a. Important adverse reactions;
b. Interactions with other medicines and allied substances;
c. Interactions with food and other substances;
d. Medication errors;
e. Effects of occupational exposure; and
f. Pharmacological class effects.

The summary on missing information should consider whether there are critical gaps in knowledge for specific safety issues or populations that use the medicine or allied substance.

16.2. Signal evaluation

This section of the PSUR/PBRER should summarise the results of evaluations of all safety signals (whether classified as important) that were closed during the reporting interval. A safety signal can be closed either because it is refuted or because it is determined to be a potential or identified risk, following evaluation. The two main categories to be included in this section are:

a. Those signals that, following evaluation, have been refuted as "false" signals based on medicinal judgement and scientific evaluation of the currently available information.
b. Those signals that, following evaluation, have been categorised as either a potential or identified risk, including lack of efficacy.

For both categories of closed signals, a concise description of each signal evaluation should be included to clearly describe the basis upon which the signal was either refuted or considered to be a potential or identified risk by the Marketing Authorisation holder.

It is recommended that the level of detail provided in the description of the signal evaluation should reflect the medicinal significance of the signal (e.g. severe, irreversible, lead to

increased morbidity or mortality) and potential public health importance (e.g. wide usage, frequency, significant use outside the recommendations of the product information) and the extent of the available evidence. Where multiple evaluations will be included under both categories of closed signals, they can be presented in the following order:

a. Closed and refuted signals.
b. Closed signals that are categorised as important potential risks.
c. Closed signals that are categorised as important identified risks.
d. Closed signals that are potential risks are not categorised as important.
e. Closed signals that are identified risks not categorised as important.

Where applicable the evaluations of closed signals can be presented by indication or population.

The description(s) of the signal evaluations can be included in this section of the PSUR/PBRER or in an appendix. Each evaluation should include the following information as appropriate:

a. Source or trigger of the signal;
b. Background relevant to the evaluation;

c. Method(s) of evaluation, including data sources, search criteria (where applicable, the specific MedDRA terms (e.g. PTs, HLTs, SOCs, etc.) or Standardised MedDRA Queries (SMQs) that were reviewed), and analytical approaches;
d. Results - a summary and critical analysis of the data considered in the signal evaluation; where integral to the assessment, this may include a description of a case series or an individual case (e.g. an index case of well documented agranulocytosis or Stevens Johnson Syndrome);
e. Discussion;
f. Conclusion.

MAH's evaluations and conclusions for refuted signals should be supported by data and clearly presented.

16.3. Evaluation of risks and new information

This section should provide a critical appraisal of new information relevant to previously recognised risks that is not already included in "Signal evaluation".

New information that constitutes a signal with respect to a previously recognised risk or previously refuted signal should be presented in the signals tabulation and evaluated in "Signal

evaluation"; if the signal is also closed during the reporting interval of the PSUR/PBRER.

Updated information on a previously recognised risk that does not constitute a signal should be included in this section. Examples include information that confirms a potential risk as an identified risk, or information which allows any other further characterisation of a previously recognised risk.

New information can be organised as follows:

a. New information on important potential risks.
b. New information on important identified risks.
c. New information on other potential risks not categorised as important.
d. New information on other identified risks not categorised as important.
e. Update on missing information.

The focus of the evaluation(s) is on new information which has emerged during the reporting interval of the PSUR/PBRER. This should be concise and interpret the impact, if any, on the understanding and characterisation of the risk. Where applicable, the evaluation will form the basis for an updated characterisation of important potential and identified risks in "Characterisation of risks" of the report. It is recommended that the level of detail of the evaluation included in this section

should be proportional to the available evidence on the risk and its medicinal significance and public health relevance.

The evaluation(s) of the new information and missing information update(s) can be included in this section of the PSUR/PBRER, or in an appendix. Each evaluation should include the following information as appropriate:

a. Source of the new information;
b. Background relevant to the evaluation;
c. Method(s) of evaluation, including data sources, search criteria, and analytical approaches;
d. Results – a summary and critical analysis of the data considered in the risk evaluation;
e. Discussion;
f. Conclusion, including whether the evaluation supports an update of the characterisation of any of the important potential and identified risks in "Characterisation of risks".

Any new information on populations exposed or data generated to address previously missing information should be critically assessed in this section. Unresolved concerns and uncertainties should be acknowledged.

16.4. Characterisation of risks

This section should characterise important identified and potential risks based on cumulative data (i.e. not restricted to the reporting interval) and describe missing information.

Depending on the nature of the data source, the characterisation of risk may include, where applicable:

a. Frequency;
b. Numbers of cases (numerator) and precision of estimate, considering the source of the data;
c. Extent of use (denominator) expressed as numbers of patients, patient-time, etc., and precision of estimate;
d. Estimate of relative risk and precision of estimate;
e. Estimate of absolute risk and precision of estimate;
f. Impact on the individual patient (effects on symptoms, quality or quantity of life);
g. Public health impact;
h. Patient characteristics relevant to risk (e.g. patient factors (age, pregnancy/lactation, hepatic/renal impairment, relevant co- morbidity, disease severity, genetic polymorphism);
i. Dose, route of administration;
j. Duration of treatment, risk period;
k. Preventability (i.e. predictability, ability to monitor for a "sentinel" adverse reaction or laboratory marker);

l. Reversibility;
m. Potential mechanism; and
n. Strength of evidence and its uncertainties, including analysis of conflicting evidence, if applicable.

When missing information could constitute an important risk, it should be included as a safety concern. The limitations of the safety database (in terms of number of patients studied, cumulative exposure or long-term use, etc.) should be discussed.

PSUR/PBRERs for products with several indications, formulations, or routes of administration, where there may be significant differences in the identified and potential risks, it may be appropriate to present risks by indication, formulation, or route of administration. Headings that could be considered include:

a. Risks relating to active substances;
b. Risks related to a specific formulation or route of administration (including occupational exposure);
c. Risks relating to a specific population; and
d. Risks associated with non-prescription use (for compounds that are available as both prescription and non-prescription products).

16.5. Effectiveness of risk minimisation

Risk minimisation activities are public health interventions intended to prevent the occurrence of an adverse drug reaction(s) associated with the exposure to a medicine or allied substance or to reduce its severity should it occur. The aim of a risk minimisation activity is to reduce the probability or severity of an adverse drug reaction. Risk minimisation activities may consist of routine risk minimisation (e.g. product labelling) or additional risk minimisation activities (e.g. Direct Healthcare Professional Communication/educational materials).

The PSUR/PBRER should contain the results of assessments of the effectiveness of risk minimisation activities relevant to the benefit-risk assessment.

Relevant information on the effectiveness and/or limitations of specific risk minimisation activities for important identified risks that have become available during the reporting interval should be summarised in this section of the PSUR/PBRER.

Insights into the effectiveness of risk minimisation activities in Zambia that may have utility in other countries or regions are of particular interest.

When required for reporting in a PSUR/PBRER, results of evaluations that became available during the reporting interval, should be provided in the PSUR/PBRER.

17. Benefit evaluation

PSUR/PBRER sections, "Important baseline efficacy and effectiveness information" and sections, "Newly identified information on efficacy and effectiveness") provide the baseline and newly identified benefit information that support the characterisation of benefit described in sections "Characterisation of benefits", that in turn supports the benefit-risk evaluation in section, "Integrated benefit-risk analysis for authorised indications".

17.1. Important baseline efficacy and effectiveness information

This section of the PSUR/PBRER summarises information on both efficacy and effectiveness of the medicine or allied substance at the beginning of the reporting interval and provides the basis for the benefit evaluation. This information should relate to authorised indications(s) of the medicine or allied substance listed in the reference product information.

For medicines and allied substances with multiple indications, populations, and/or routes of administration, the benefit should be characterised separately by these factors when relevant.

The level of detail provided in this section should be sufficient (Refer to ICH) to support the characterisation of benefit in the PSUR/PBRER sections, "Characterisation of benefits" and the benefit- risk assessment in section, "Integrated benefit-risk analysis for authorised indications".

17.2. Newly identified information on efficacy and effectiveness

For some products, additional information on efficacy or effectiveness in authorised indications may have become available during the reporting interval. Such information should be presented in this section of the PSUR/PBRER. For authorised indications, new information on efficacy and effectiveness under conditions of actual use should also be described in this section, if available. New information on efficacy and effectiveness in uses other than the authorised indications should not be included unless relevant for the benefit-risk evaluation in the authorised indications.

Information on indications newly authorised during the reporting interval should also be included in this section. The level of detail provided in this section should be sufficient to support the characterisation of benefit in sections "Characterisation of benefits" and the benefit-risk assessment in section "Integrated benefit-risk analysis for authorised indications".

In this section, particular attention should be given to vaccines, anti- infective agents or other medicines and allied substances where changes in the therapeutic environment may impact on efficacy/effectiveness over time.

17.3. Characterisation of benefits

This section provides an integration of the baseline benefit information and the new benefit information that has become available during the reporting interval, for authorised indications.

The level of detail provided in this section should be sufficient to support the analysis of benefit-risk in section, "Integrated benefit-risk analysis for authorised indications."

When there are no new relevant benefit data, this section should provide a characterisation of the information in sections, "Important baseline efficacy and effectiveness information."

When there is new positive benefit information and no significant change in the risk profile in this reporting interval, the integration of baseline and new information in this section should be succinct.

This section should provide a concise but critical evaluation of the strengths and limitations of the evidence on efficacy and effectiveness, considering the following when available:

a. A brief description of the strength of evidence of benefit, considering comparator(s), effect size, statistical rigor, methodological strengths and deficiencies, and consistency of findings across trials/studies;
b. New information that challenges the validity of a surrogate endpoint, if used;
c. Clinical relevance of the effect size;
d. Generalisability of treatment response across the indicated patient population (e.g. information that demonstrates lack of treatment effect in a sub-population);
e. Adequacy of characterization of dose-response;
f. Duration of effect;
g. Comparative efficacy; and
h. A determination of the extent to which efficacy findings from clinical trials are generalisable to patient populations treated in medicinal practice.

18. Integrated benefit-risk analysis for authorised indications

The MAH should provide in this PSUR/PBRER section an overall appraisal of the benefit and risk of the medicine or allied substance as used in clinical practice. Whereas sections "Characterisation of risks" and sections "Characterisation of

benefits" present the risks and benefits, this section should provide a critical analysis and integration of the key information in the previous sections and should not simply duplicate the benefit and risk characterisation presented in the sections mentioned above.

18.1. Benefit-risk context - medicinal need and important alternatives

This section of the PSUR/PBRER should provide a brief description of the medicinal need for the medicine or allied substance in the authorised indications and summarised alternatives (medicinal, surgical or other; including no treatment).

18.2. Benefit-risk analysis evaluation

A benefit-risk balance is specific to an indication and population. Therefore, for products authorised for more than one indication, benefit-risk balances should be evaluated and presented by each indication individually. If there are important differences in the benefit-risk balance among populations within an indication, the benefit-risk evaluation should be presented by population, if possible.

The benefit-risk evaluation should be presented and discussed in a way that facilitates the comparison of benefits and risks and should consider the following points:

a. Whereas previous sections should include all important benefit and risk information, not all benefits and risks contribute importantly to the overall benefit-risk evaluation, therefore, the key benefits and risks considered in the evaluation should be specified. The key information presented in the previous benefit and risk section should be carried forward for integration in the benefit risk evaluation.

b. Consider the context of use of the medicine or allied substance: the condition to be treated, prevented, or diagnosed; its severity and seriousness; and the population to be treated (relatively healthy; chronic illness, rare conditions).

c. With respect to the key benefit(s), consider its nature, clinical importance, duration, and generalizability, as well as evidence of efficacy in non-responders to other therapies and alternative treatments. Consider the effect size. If there are individual elements of benefit, consider all (e.g. for therapies for rheumatoid arthritis: reduction of symptoms and inhibition of radiographic progression of joint damage).

d. With respect to risk, consider its clinical importance, (e.g. nature of toxicity, seriousness, frequency, predictability, preventability, reversibility, impact on patients), and whether it arose from clinical trials in

unauthorized indications or populations, off-label use, or misuse.

e. The strengths, weaknesses, and uncertainties of the evidence should be considered when formulating the benefit-risk evaluation. Describe how uncertainties in the benefits and risks impact the evaluation. Limitations of the assessment should be discussed.

Provide a clear explanation of the methodology and reasoning used to develop the benefit-risk evaluation:

a. The assumptions, considerations, and judgement or weighting that support the conclusions of the benefit-risk evaluation should be clear.
b. If a formal quantitative or semi-quantitative assessment of benefit-risk is provided, a summary of the methods should be included.
c. Economic considerations (e.g. cost-effectiveness) should not be considered in the benefit-risk evaluation.

When there is important new information or an ad hoc PSUR/PBRER has been requested, a detailed benefit-risk analysis should be presented based on cumulative data. Conversely, where little new information has become available during the reporting interval, the primary focus of the benefit-risk evaluation might consist of an evaluation of updated interval safety data.

19. Conclusions and actions

A PSUR/PBRER should conclude with the implications of any new information that arose during the reporting interval in terms of the overall evaluation of benefit-risk for each authorised indication, as well as for relevant subgroups, if appropriate.

Based on the evaluation of the cumulative safety data and the benefit- risk analysis, the MAH should assess the need for changes to the reference product information and propose changes as appropriate.

In addition, and as applicable, the conclusions should include preliminary proposal(s) to optimise or further evaluate the benefit-risk balance for further discussion with the Authority. This may include proposals for additional risk minimisation activities.

For products with a safety monitoring or risk management plan, the proposals should also be considered for incorporation into the safety monitoring plan and/or risk minimisation plan, as appropriate.

Based on the evaluation of the cumulative safety data and the benefit- risk analysis, the MAH should draw conclusions in the PSUR/PBRER as to the need for changes and/or actions, including implications for the approved summary of product

characteristics for the product(s) for which the PSUR/PBRER is submitted.

Proposed changes to the reference product information should be described in this section of the PSUR/PBRER. The appendix should include proposals for summary of product information and package leaflet together with information on ongoing changes when applicable.

20. Appendices to the PSUR/PBRER

A PSUR/PBRER should contain the following appendices as appropriate, numbered as follows:

i. Reference information.
ii. Cumulative summary tabulations of serious adverse events from clinical trials; and cumulative and interval summary tabulations of serious and non- serious adverse reactions from post-marketing data sources.
iii. Tabular summary of safety signals (if not included in the body of the report).
iv. Listing of all the MAH-sponsored interventional and non-interventional studies with the primary aim of identifying, characterising, or quantifying a safety hazard or confirming the safety profile of the medicine or allied substance, or of measuring the effectiveness of

risk management measures, in case of non-interventional studies.

v. List of the sources of information used to prepare the PSUR/PBRER.

Mapping signals and risks to PSUR/PBRER sections

The information on signals and risks should be mapped in a flow chart.

MAHs should have in place structures and processes for the preparation, quality control, review and submission of PSUR/PBRERs including follow-up during and after their assessment. These structures and processes should be described by means of written policies and procedures in the MAH's quality management system.

There are a number of areas in the safety monitoring process that can directly impact the quality of PSUR/PBRERs, some examples are case management of spontaneous and study reports, literature screening, signal management, additional safety monitoring and post-marketing research activities, procedures for integration of information on benefits and risks from all available data sources and maintenance of product information. The quality management system should describe the links between the processes, the communication channels and the responsibilities with the aim of gathering all the

relevant information to produce PSUR/PBRERs. There should be documented procedures including quality control checks in place to check the accuracy and completeness of the data presented in the PSUR/PBRERs. In ensuring completeness of data, a documented template or plan for drawing data from various data sources could be developed. The importance of an integrated approach to benefit-risk evaluation should underpin processes and cross departmental input to PSUR/PBRER preparation.

The PSUR/PBRER should also contain an assessment of specific safety issues requested by the Authority in accordance with agreed timelines and procedures. The MAH should have mechanisms in place to ensure that the requests made by the Authority during the time of their PSUR/PBRER assessment are properly addressed.

The provision of the data included in the summary tabulations should undergo source data verification against the MAH's safety database to ensure accuracy of the number of events/reactions provided. The process for querying the safety database, the parameters used for the retrieval of the data and the quality control performed should be properly documented.

Quality management systems for PSUR/PBRERs at the level of MAHs

An appropriate quality management system should be in place to avoid failure to comply with PSUR/PBRER requirements such as:

a. Non-submission: complete non-submission of PSUR/PBRERs, submission outside the correct submission schedule or outside the correct time frames (without previous agreement with the Authority);
b. Unjustified omission of information required;
c. Poor quality reports: poor documentation or insufficient information or evaluation provided to perform a thorough assessment of the new safety information, signals, risk evaluation, benefit evaluation and integrated benefit-risk analysis, misuse not highlighted, absence of use of standardised medicinal terminology and inappropriate dismissal of cases with no reported risk factors in cumulative reviews;
d. Submission of a PSUR/PBRER where previous requests from the Authority have not been addressed;
e. Failure to provide an explicit evaluation of the benefit-risk balance of the medicine or allied substance;
f. Failure to provide adequate proposals for the local authorised product information.

Any significant deviation from the procedures relating to the preparation or submission of PSUR/PBRERs should be documented and the appropriate corrective and preventive action should be taken. This documentation should always be available.

When MAHs are involved in contractual arrangements (e.g. licensor-licensee) respective responsibilities for preparation and submission of the PSUR/PBRER to the Authority should be clearly specified in the written agreement.

When the preparation of the PSUR/PBRER is delegated to third parties, the MAH should ensure that they are subject to a quality management system compliant with the current legislation. Explicit procedures and detailed agreements should exist between the MAH and third parties. The agreements may specifically detail the options to audit the PSUR/PBRER preparation process.

Training of staff members related to the PSUR/PBRER process

For all organisations, it is the responsibility of the person responsible for the Safety Monitoring System to ensure that the personnel, including safety monitoring, medicinal and quality personnel involved in the preparation, review, quality control, submission and assessment of PSUR/PBRERs are adequately

qualified, experienced and trained according to the applicable guidelines (e.g. ICH E2C(R2)). The appropriate specific training for the different processes, tasks and responsibilities relating to the PSUR/PBRER should be in place.

Training to update knowledge and skills should also take place as necessary. Training should cover regulations, guidelines, scientific evaluation and written procedures related to the PSUR/PBRER process. Training records should demonstrate that the relevant training was delivered prior to performing PSUR/PBRER-related activities

8. POST AUTHORISATION SAFETY STUDIES

8.1. A post-authorisation safety study (PASS) is defined as any study relating to an authorised medicine or allied substance conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicine or allied substance, or of measuring the effectiveness of risk management measures. This includes studies that may have commenced prior to registration that are on-going after the product has been registered.

8.2. A PASS may be initiated, managed or financed by MAH voluntarily, or pursuant to an obligation imposed by the Authority.

8.3. This Section concerns PASS which are clinical trials or non-Interventional studies and do not address non-clinical safety studies.

8.4. A PASS is non-interventional if the following requirements are cumulatively fulfilled:

8.4.1. The medicine or allied substance is prescribed in the usual manner in accordance with the terms of the Marketing Authorisation.

8.4.2. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the

medicine is clearly separated from the decision to include the patient in the study; and

8.4.3. No additional diagnostic or monitoring procedures are applied to the patients, and epidemiological methods are used for the analysis of collected data.

8.5. Non-interventional studies are defined by the methodological approach used and not by its scientific objectives. Non-interventional studies include database research or review of records where all the events of interest have already happened (this may include case-control, cross-sectional, cohort or other study designs making secondary use of data). Non-interventional studies also include those involving primary data collection (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care), provided that the conditions set out above are met. In these studies, interviews, questionnaires and blood samples may be performed as part of normal clinical practice.

8.6. The purpose of this Section is to:

8.6.1. Provide general guidance for the transparency, scientific standards and quality standards of non-interventional PASS conducted by MAHs voluntarily or pursuant to an obligation imposed by the Authority;

8.6.2. Describe procedures whereby the Authority may impose to MAH an obligation to conduct a clinical trial

or a non-interventional study, and the impact of this obligation on the risk management system;

8.6.3. Describe procedures that apply to non-interventional PASS imposed as an obligation for the protocol oversight and reporting of results and for changes to the Marketing Authorisation following results.

8.7. Structures and processes

8.7.1. This section applies to non-interventional PASS which are initiated, managed or financed by MAH as well as those conducted by a third party on behalf of the MAH. It involves 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.

8.7.2. Legal requirements which are applicable to studies conducted pursuant to an obligation are recommended to studies conducted voluntarily to support the same level of transparency, scientific standards and quality standards for all PASS. This applies, for example, to the format of study protocols, abstracts and final study reports and communication of the study information to the Authority.

8.8. Principles

8.8.1. A post-authorisation study should be classified as PASS when the main aim for initiating the study includes any of the following objectives:

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

ii. To evaluate risks of a medicine or allied substance used in patient populations for which safety information is limited or missing (e.g. pregnant women, specific age groups, patients with renal or hepatic impairment);

iii. To evaluate the risks of a medicine or allied substance after long-term use;

iv. To provide evidence about the absence of risks;

v. To assess patterns of drug utilisation that add knowledge on the safety of the medicine or allied substance (e.g. indication, dosage, co- medication, medication errors);

vi. To measure the effectiveness of a risk minimisation activity.

8.8.2. The PASS design should be appropriate to address the study objective(s), for example, a systematic literature

review or a meta- analysis may be considered as PASS depending on their aim.

8.8.3. Good Clinical Practice guidelines (see ICH E6) should be considered by MAHs and investigators for the development of study protocols, conduct of studies and writing of study reports as evaluated by the Authority.

8.8.4. For studies that are funded by MAH, including studies developed, conducted or analysed fully or partially by investigators who are not employees of the MAH, the MAH should ensure that the investigators are qualified by education, training and experience to perform their tasks. The research contract between the MAH and investigators should ensure that the study meets its regulatory obligations while permitting their scientific expertise to be exercised throughout the research process.

8.8.5. In the research contract, the MAH should consider and address the following aspects:

i. Rationale, main objectives and brief description of the intended methods of the research to be carried out by the investigator(s);
ii. Rights and obligations of the investigator(s) and MAH;
iii. Clear assignment of tasks and responsibilities;
iv. Procedure for achieving agreement on the study protocol;

v. Provisions for meeting the MAH's safety monitoring obligations, including the reporting of adverse reactions and other safety data by investigators

vi. Intellectual property rights arising from the study and access to study data;

vii. Storage and availability of analytical data set and statistical programmes for audit and inspection;

viii. Communication strategy for the scheduled progress and final reports; and

ix. Publication strategy of interim and results.

8.8.6. Non-interventional post-authorisation safety studies should not be performed where the act of conducting the study promotes the use of a medicine or allied substances. This requirement applies to all studies and to all activities performed in the study, including studies conducted by the personnel of the MAH and by third parties on behalf of the MAH.

8.8.7. Payments to healthcare professionals for participating should be restricted to compensation for time and expenses incurred.

8.9. Study registration

8.9.1. To support transparency on interventional and non-interventional PASS conducted voluntarily or pursuant to an obligation and to facilitate exchange of safety monitoring information between the Authority and

MAHs, the MAH should make available the study information, before the start of data collection, and notify the Authority. Any amendment to the study protocol should be submitted to the ethics committee that originally approved the protocol and the Authority. Final study report should be submitted to the Authority within 12 months after study completion.

8.10. Study protocol

8.10.1. All post-authorisation safety studies must have a written study protocol before the study commences. The study should follow a scientifically sound protocol developed by individuals with appropriate scientific background and experience. The good clinical practice regulation and guidelines of the Authority should be followed to ensure the well-being and rights of the participants. The MAH should obtain prior approval of the protocol from the Authority.

8.10.2. To ensure compliance of the MAH with its safety monitoring obligations, the qualified person responsible for pharmacovigilance (LQPPV) or his/her delegate should be involved in the review and sign-off of study protocols conducted in Zambia.

8.11. Format and content of the study protocol

8.11.1. The study protocol should include the following information:

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

ii. MAH: name, address and contact details

iii. Responsible parties: names, titles, qualifications, addresses, and affiliations of all main responsible parties, including the main author(s) of the protocol, the principal investigator, a coordinating investigator for multiple centre study. A list of all collaborating institutions and principal investigators should be made available to the Authority upon request.

iv. Abstract: stand-alone summary of the study protocol including the following sections:

   a) Title with subtitles including version and date of the protocol and name and affiliation of main author
   b) Rationale and background
   c) Research question and objectives
   d) Study design
   e) Population
   f) Variables
   g) Data sources
   h) Sample size
   i) Data analysis

j) Milestones

8.11.2. 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.

8.11.3. Milestones: table with planned dates for the following milestones:

i. Start of data collection
ii. End of data collection
iii. Study progress report(s)
iv. Interim report(s) of study results, where applicable, in line with phases of data analyses
v. Final report on study results; and
vi. Any other important timelines in the conduct of the study

8.11.4. 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.

8.11.5. 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.

8.11.6. Research methods: description of the research methods, including:

i. Study design: overall research design and rationale for this choice.

ii. Setting: study population defined in terms of persons, place, 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.

iii. 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.

iv. 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 completed, a summary of the results should be reported. Involvement of any expert committee 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.

v. Sample size: any projected sample 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.

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

vii. 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.

viii. 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 statistical programmes. As appropriate, certification and/or qualifications of any supporting laboratory or research groups should be included.

ix. 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 errors. The likely success of efforts made to reduce errors should be discussed.

x. Protection of human participants: safeguards to comply with the good clinical practice regulation requirements of the Authority for ensuring the well-being and rights of participants in non-interventional post- authorisation safety studies.

xi. 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.

xii. Plans for disseminating and communicating study results, including any plans for submission of progress reports and final reports.

xiii. References

8.11.7. Feasibility studies that were carried out to support the development of the protocol, for example, the testing of

a questionnaire or simple counts of medicinal events or prescriptions in a database to determine the statistical precision of the study, should be reported in the appropriate section of the study protocol with a summary of their methods and results. The full report should be made available to the Authority upon request.

8.11.8. Feasibility studies that are part of the research process should be described in the protocol, for example, a pilot evaluation of the study questionnaire(s) used for the first set of patients recruited into the study.

8.11.9. 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, informed consent), with clear document references.

8.12. Substantial amendments to the study protocol

8.12.1. The study protocol should be amended and updated as needed throughout the course of the study. Any substantial amendments to the protocol after the study start should be documented in the protocol in a traceable and auditable way including the dates of the changes. If changes to the protocol lead to the study being considered an interventional clinical trial, approval shall be sought from the Authority and the

study conducted in accordance with the Clinical Trial regulations and guidelines.

8.13. Reporting of safety monitoring data to the Authority

8.13.1. Data relevant to the benefit-risk balance of the product

i. The MAH should monitor the data generated while the study is being conducted and consider their implications for the benefit-risk balance of the medicine or allied substance concerned. Any new information that may affect the benefit-risk balance of the medicine or allied substance should be communicated immediately in writing as an Emerging Safety Issue to the Authority. Information affecting the benefit-risk balance of the medicine or allied substance may include that arising from an analysis of adverse reactions and aggregated data.

ii. This communication should not affect information on the results of studies which should be provided by means of periodic safety update reports (PSUR/PBRERs) and in RMP updates, where applicable.

8.14. Reporting of adverse reactions/adverse events

8.14.1. Adverse reactions/adverse events should be reported to the Authority in accordance with these Guidelines. Procedures for the collection, management (including a review by the MAH) and reporting of suspected adverse reactions/adverse events should be put in place and summarised in the study protocol. If appropriate, reference can be made to the Safety Monitoring System Master File but details specific to the study should be described in this section. For study designs where expedited reporting is not required, this should be stated in the study protocol.

8.15. Study reports

8.15.1. Progress reports

i. Progress reports may be requested by the Authority. Requests for progress reports may be made at any time during the study conduct. This may be guided by the communication of benefit-risk information arising from the study or the need for information about the study progress in the context of regulatory procedures or important safety communication about the product.

ii. The timing of the progress reports should be agreed with the Authority and specified in the study

protocol when they have been agreed before the study commences. Study progress should also be reported in any periodic safety update reports (PSUR/PBRERs) and risk management plan (RMP), where applicable.

iii. The content of the progress report should follow a logical sequence and should include all the available data that are judged relevant for the progress of the study, for example, number of patients who have entered the study, number of exposed patients or number of patients presenting the outcome, problems encountered and deviations from the expected plan. The progress report may also include any interim report on study results. After reviewing the report, additional information may be requested.

8.15.2. Final study report

i. The final study report should be submitted as soon as possible within 12 months of the end of data collection. End of data collection means the precise date when the analytical dataset is fully available for synthesising the study findings. If a study is discontinued, a final report should be submitted and the reasons for terminating the study should be provided.

ii. The final study report should include the following information:

a) Title: title including a commonly used term indicating the study design; sub-titles with date of final report and name and affiliation of main author.
b) Abstract: stand-alone summary in the format presented in section 8.16
c) MAH: name and address of the MAH
d) Investigators: names, titles, degrees, addresses and affiliations of all main responsible parties, including the main author(s) of the protocol, the principal investigator, a coordinating investigator for multiple centre study. A list of all collaborating institutions and principal investigators should be made available to the Authority upon request.
e) Milestones: planned and actual dates for the following milestones:
   (i) Start of data collection
   (ii) End of data collection or date of early termination, if applicable, with reasons for termination
   (iii) Study progress report(s)
   (iv) Interim report(s) of study results, where applicable

(v) Final report on study results

(vi) Any other important milestone applicable to the study, including date of protocol approval by an Ethics Committee, and date of study registration in the local PASS Register.

f) Rationale and background: short description of the safety concern(s) that led to the study being initiated or imposed, and short critical review of relevant published and unpublished data evaluating pertinent information and gaps in knowledge that the study is intended to fill.

g) Research question and objectives: research question and research objectives, including any pre-specified hypotheses, as stated in the study protocol.

h) Amendments and updates to the protocol: list of any substantial amendments and update to the initial study protocol after the start of data collection, including a justification for each amendment or update.

8.15.3. Research methods

i. Study design: key elements of the study design and the rationale for this choice.

ii. Setting: setting, locations, and relevant dates for the study, including periods of recruitment, follow-up,

and data collection. In case of a systematic review or meta-analysis, study characteristics used as criteria for eligibility, with rationale.

iii. Participants: any source population and eligibility criteria of study participants. Sources and methods of selection for participants should be provided, including, where relevant methods for case ascertainment, as well as number of, and reasons for dropouts.

iv. Variables: all outcomes, exposures, predictors, potential confounders, and effect modifiers, including operational definitions and diagnostic criteria, if applicable.

v. Data sources and measurement: for each variable of interest, sources of data and details of methods of assessment and measurement. If the study has used 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. In case of a systematic review or meta- analysis, description of all information sources, search strategy, methods for selecting studies, methods of data extraction and any processes for obtaining or confirming data from investigators.

vi. Bias: any efforts to assess and address potential sources of bias.

vii. Study size: study size, rationale for any sample size calculation and any method for attaining projected study size.

viii. Data transformation: transformations, calculations or operations on the data, including how quantitative data were handled in the analyses and which groupings were chosen and why.

ix. Statistical methods: description of:

a) Main summary measures.

b) Statistical methods applied to the study, including those used to control for confounding and, for meta-analyses, methods for combining results of studies.

c) Any methods used to examine subgroups and interactions.

d) How missing data was addressed.

e) Any sensitivity analyses.

f) Any amendment to the plan of data analysis included in the study protocol, with a rationale for the change.

x. Quality control: mechanisms to ensure data quality and integrity.

xi. Results: presentation of tables, graphs, and illustrations to present the pertinent data and reflect the analyses performed. Both unadjusted and adjusted results should be presented. Precision of estimates should be quantified using confidence intervals. This section should include the following sections:

a) Participants: numbers of study participants at each stage of study, e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed, and reasons for non-participation at any stage. In the case of a systematic review or meta-analysis, the number of studies screened, assessed for eligibility and included in the review with reasons for exclusion at each stage.

b) Descriptive data: characteristics of study participants, information on exposures and potential confounders and number of participants with missing data for each variable of interest. In case of a systematic review or meta-analysis, characteristics of each study from which data were extracted (e.g. study size, follow-up).

c) Outcome data: numbers of participants across categories of main outcomes.

d) Main results: unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). If relevant, estimates of relative risk should be translated into absolute risk for a meaningful period.

e) Other analyses: other analyses done, e.g. analyses of subgroups and interactions, and sensitivity analyses.

f) Adverse events and adverse reactions: summary of all adverse events/adverse reactions reported in the study. For certain study designs such as case-control or retrospective cohort studies, particularly those involving electronic health care records, systematic reviews and meta-analyses where it is not feasible to make a causality assessment at the individual case level, this should be stated.

8.15.4. Discussion

i. Key results: key results with reference to the study objectives, prior research in support of and conflicting with the findings of the completed post-authorisation safety study, and, where relevant,

impact of the results on the benefit-risk balance of the product.

ii. Limitations: limitations of the study taking into account circumstances that may have affected the quality or integrity of the data, limitations of the study approach and methods used to address them (e.g., response rates, missing or incomplete data, imputations applied), sources of potential bias and imprecision and validation of the events. Both direction and magnitude of potential biases should be discussed.

iii. Interpretation: interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies and other relevant evidence.

iv. Generalizability: the generalizability (external validity) of the study results.

v. References.

vi. Other information: any additional or complementary information on specific aspects not previously addressed.

8.16. The abstract of the final study report should include a summary of the study methods and findings presented in the following format:

8.16.1. Title, with subtitles including date of the abstract and name and affiliation of main author;

8.16.2. Keywords (not more than five keywords indicating the main study characteristics);

8.16.3. Rationale and background;

8.16.4. Research question and objectives;

8.16.5. Study design;

8.16.6. Setting;

8.16.7. Participants and study size, including dropouts;

8.16.8. Variables and data sources;

8.16.9. Results;

8.16.10. Discussion (including, where relevant, an evaluation of the impact of study results on the risk- benefit balance of the product);

8.16.11. MAH;

8.16.12. Names and affiliations of principal investigators.

8.17. Publication of study results

8.17.1. For studies that are fully or partially conducted by investigators who are not employees of the MAH, the MAH and the investigator should agree in advance to a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. The MAH should be entitled to view the results and interpretations

included in the manuscript and provide comments prior to submission of the manuscript for publication.

8.18. Regulatory submission of manuscripts accepted for publication

8.18.1. To allow the Authority to review in advance the results and interpretations to be published, the MAH should communicate to the Authority the final manuscript of the article within two weeks after first acceptance for publication.

8.19. Data protection

8.19.1. MAHs and investigators should follow relevant national legislation in Zambia.

8.19.2. For PASS imposed as an obligation, the MAH should ensure that all study information is handled and stored to allow for accurate reporting, interpretation and verification of that information and should ensure that the confidentiality of the records of the study subjects remains protected. This provision should also be applied to PASS voluntarily initiated, managed or financed by the MAH.

8.20. Quality management systems, audits and inspections

8.20.1. The MAH should ensure the fulfilment of its safety monitoring obligations in relation to the study and that this can be audited, inspected and verified. For PASS imposed as an obligation, the MAH should ensure that the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection. This provision should also be applied to PASS voluntarily initiated, managed or financed by the MAH.

8.21. Impact on the risk management system

8.21.1. Non-interventional PASS imposed as an obligation or required to investigate safety concern of the RMP should be described in the RMP. Protocols for studies in the safety monitoring plan should be provided in RMP (annex 6) until submission of the final study report to the Authority. Studies looking at the effectiveness of risk minimisation measures should be included in the safety monitoring plan against the specific safety concern(s) as well as described in detail in the risk minimisation plan.

8.21.2. Other non-interventional PASS which are not obligations or required studies in the RMP, but which could provide relevant information on the safety profile of the product should be listed in the RMP "Summary table of additional safety monitoring activities.

8.22. Conditions for imposing PASS on MAH

8.22.1. The need for a PASS could be identified by the Authority during a post-authorisation regulatory procedure, for example, an extension or a variation to a Marketing Authorisation or a renewal procedure.

8.23. Request for a post-authorisation safety study due to an emerging safety concern

8.23.1. After the granting of the Marketing Authorisation, the Authority may impose on the MAH an obligation to conduct a post- authorisation safety study if there are concerns about the risk of the authorised medicine or allied substance, for example following evaluation of a safety signal.

8.24. Joint post-authorisation safety studies

8.24.1. If safety concerns apply to more than one medicine or allied substance, the Authority will encourage the MAHs concerned to conduct a joint PASS.

8.24.2. A joint PASS may also be necessary where there are limited patients (rare diseases), or the adverse reaction is rare. Requests to the MAHs should contain the justification for the request for a joint study and the elements of the study design that support a joint protocol. Upon request from the MAHs, the Authority may organise a pre-submission meeting to provide suggestions for a joint study proposal and facilitate agreement in developing a joint protocol. If a joint protocol is not voluntarily agreed and different proposals are submitted, the Authority may define, either a common core protocol or key elements (for example, the study design, the study population and the definition of exposure and outcomes) which each MAH will have to implement in the study protocol to be submitted to the Authority.

8.25. Written observations in response to the imposition of an Obligation

8.25.1. Within 30 days of receipt of the written notification of the obligation, the MAH may request the opportunity to present written observations in response to the imposition of the obligation. The Authority will specify a time limit for the provision of these observations.

Based on the written observations submitted by the MAH, the Authority may withdraw or confirm the obligation. When the obligation is confirmed, the Marketing Authorisation should be subject to variation to include the obligation as a condition and the risk management plan (RMP) should be updated accordingly.

8.26. Impact on the risk management system

8.26.1. All post-authorisation safety studies imposed as a condition on the Marketing Authorisation will be described in the RMP and their results provided in the PSUR/PBRER following completion of the final report, where applicable.

8.26.2. All relevant sections of the RMP should be amended to document the conduct of the study, including the safety specification, the safety monitoring plan, the risk minimisation plan and the summary of activities, as appropriate. A copy of the study protocol approved by the Authority should be provided as an annex in the RMP. When a RMP does not exist, a new RMP should be developed referring to the post- authorisation safety study.

8.27. Regulatory supervision of non-interventional post-authorisation safety studies

8.27.1. Non-interventional PASS conducted pursuant to obligations imposed by the Authority are supervised and assessed by the Authority.

8.28. Roles and responsibilities of the MAH

8.28.1. Following the imposing of the obligation to conduct a non-interventional PASS as a condition to the Marketing Authorisation, the MAH should develop a study protocol and submit it to the Authority for review.

8.28.2. The MAH has the responsibility to ensure that the study is not a clinical trial. If the study is a non-interventional study, the MAH should ensure that the study meets all the requirements applicable to non-interventional PASS. The MAH should ensure the fulfilment of its safety monitoring obligations in relation to the study and that this can be audited, inspected and verified.

8.28.3. The study may commence only when the written authorisation from the Authority has been issued.

8.28.4. Prior to submission of the protocol, the MAH may submit a request to the Authority for a pre-submission meeting with the Authority to clarify specific aspects of the requested study (such as study objectives, study

population, definition of exposure and outcomes) and to facilitate the development of the protocol.

8.28.5. After a study has commenced, the MAH should submit any substantial amendments to the protocol to the Authority, before their implementation.

8.28.6. The MAH may be requested to submit study progress reports to the Authority.

8.28.7. Upon completion of the study, the MAH should submit a final study report, including a public abstract, to the Authority as soon as possible and not later than 12 months after the end of data collection, unless a written waiver has been granted. The final study report should follow the format recommended earlier.

8.28.8. The MAH should submit the study protocol, the abstract of the final study report and the final study report.

8.29. Changes to the Marketing Authorisation following results from a non- interventional post-authorisation safety study

8.29.1. The MAH should evaluate whether the study results have an impact on the Marketing Authorisation and should, if necessary, submit to the Authority an application for amendment to the Marketing Authorisation.

8.29.2. Following the review of the final study report, the Authority may recommend variation or suspend or revoke the Marketing Authorisation.

9. PHARMACOVIGILANCE AUDITS

9.1. This Section provides guidance on planning and conducting audits and outlines the general structures and processes that should be followed to identify the most appropriate pharmacovigilance audit activities.

9.2. The Section further describes the steps which can be undertaken by MAHs to plan, conduct and report upon individual pharmacovigilance audit activities. It also provides an outline of the general quality management system and record management practices for pharmacovigilance audit processes.

9.3. Structures, processes and objectives of Pharmacovigilance Audits

9.3.1. Pharmacovigilance audit activities should verify, by examination and evaluation of objective evidence, the appropriateness and effectiveness of the implementation and operation of a Safety Monitoring System, including its quality management system for pharmacovigilance activities.

9.3.2. In general, an audit is a systematic, disciplined, independent and documented process for obtaining evidence and evaluating the evidence objectively to

determine the extent to which the audit criteria are fulfilled, contributing to the improvement of risk management, control and governance processes.

9.3.3. Audit evidence consists of records, statements or other information, which are relevant to the audit criteria and verifiable. Audit criteria are, for each audit objective, the standards of performance and control against which the auditee and its activities will be assessed. In the context of pharmacovigilance, audit criteria should reflect the requirements for the Safety Monitoring System, including its quality management system for pharmacovigilance activities, as found in this document and the regulation.

9.4. The risk-based approach to pharmacovigilance audits

9.4.1. A risk-based approach is one that uses techniques to determine the areas of risk, where risk is defined as the probability of an event occurring that will have an impact on the achievement of objectives, taking account of the severity of its outcome and/or likelihood of non-detection by other methods.

9.4.2. The risk-based approach to audits focuses on the areas of highest risk to the organisation's Safety Monitoring System, including its quality management system for pharmacovigilance activities. In the context of

pharmacovigilance, the risk to public health is of prime importance. Risk can be assessed at the following stages:

i. Strategic level audit planning resulting in an audit strategy (long term approach), which should be endorsed by the management;
ii. Tactical level audit planning resulting in an audit programme, setting audit objectives, and the extent and boundaries, often termed as scope, of the audits in that programme; and
iii. Operational level audit planning resulting in an audit plan for individual audit activities, prioritising audit tasks based on risk and utilising risk-based sampling and testing approaches, and reporting audit findings in line with their relative risk level and audit recommendations.

9.4.3. Risk assessment should be documented appropriately for the strategic, tactical and operational planning of pharmacovigilance audit activity in the organisation.

9.5. Strategic level audit planning

9.5.1. The audit strategy is a high-level statement of how the audit activities will be delivered over a period, longer than the annual programme, usually for a period of 2-5

years. The audit strategy includes a list of audits that could reasonably be performed. The audit strategy is used to outline the areas highlighted for audit, the audit topics as well as the methods and assumptions (including e.g. risk assessment) on which the audit programme is based.

9.5.2. The audit strategy should cover the governance, risk management and internal controls of all parts of the Safety Monitoring System including:

i. All pharmacovigilance processes and tasks;
ii. The quality management system for pharmacovigilance activities;
iii. Interactions and interfaces with other departments, as appropriate;
iv. Pharmacovigilance activities conducted by affiliated organisations or activities delegated to another organisation (e.g. MAH affiliates or third parties, such as contract organisations and other vendors).

9.5.3. This is a non-prioritised, non-exhaustive list of examples of risk factors that could be considered for the purpose of a risk assessment:

i. Major re-organisation or other re-structuring of the Safety Monitoring System, mergers, acquisitions

(specifically for MAHs, this may lead to a significant increase in the number of products for which the system is used);

ii. Change in key managerial function(s);

iii. Risk for availability of adequately trained and experienced pharmacovigilance staff, e.g. due to significant turnover of staff, deficiencies in training processes, re-organisation, increase in volumes of work;

iv. Significant changes to the system since the time of a previous audit, e.g. introduction of a new database(s) for pharmacovigilance activities or of a significant upgrade to the existing database(s), changes to processes and activities to address new or amended regulatory requirements;

v. First medicine or allied substance on the market (for MAH);

vi. Medicine or allied substance(s) on the market with specific risk minimisation measures or other specific safety conditions such as requirements for additional monitoring;

vii. Criticality of the process, e.g. for MAHs: how critical is the area/process to proper functioning of the Safety Monitoring System. When deciding when to audit an affiliate or third party, the MAH

should consider the nature and criticality of the pharmacovigilance activities that are being performed by an affiliate or third party on behalf of the MAH, in addition to considering the other factors included in this list;

viii. Outcome of previous audits, e.g. has the area/process ever been audited (if not, then this may need to be prioritised depending on criticality); if the area/process has previously been audited, the audit findings are a factor to consider when deciding when to re-audit the area/process, including the implementation of agreed actions;

ix. Identified procedural gaps relating to specific areas/processes;

x. Other information relating to compliance with the regulation

e.g for MAHs: information from compliance metrics from inspections, from complaints, from other external sources, e.g. audits;

xi. Other organisational changes that could negatively impact on the area/process, e.g. if a change occurs to a support function (such as information technology support) this could negatively impact pharmacovigilance activities.

9.6. Tactical level audit planning

9.6.1. An audit programme is a set of one or more audits planned for a specific timeframe, normally for a year. It should be prepared in line with the long-term audit strategy. The audit programme should be approved by the management with overall responsibility for operational and governance structure.

9.6.2. The risk-based audit programme should be based on an appropriate risk assessment and should focus on:

i. The quality management system for pharmacovigilance activities;
ii. Critical pharmacovigilance processes;
iii. Key control systems relied on, for pharmacovigilance activities;
iv. Areas identified as high risk, after controls have been put in place or mitigating action taken.

9.6.3. The risk-based audit programme should also consider historical areas with insufficient past audit coverage, and high-risk areas identified by and/or specific requests from management and/or persons responsible for pharmacovigilance activities.

9.6.4. The audit programme documentation should include a brief description of the plan for each audit to be delivered, including an outline of scope and objectives.

9.6.5. The rationale for the timing, periodicity and scope of the individual audits which form part of the audit programme should be based on the documented risk assessment. However, risk-based pharmacovigilance audit(s) should be performed at regular intervals, which are in line with the Authority's requirements.

9.6.6. Changes to the audit programme may happen and will require proper documentation.

9.7. Operational level audit planning and reporting

Planning and fieldwork

9.7.1. The MAHs should ensure that written procedures are in place regarding the planning and conduct of individual audits that will be delivered. Timeframes for all the steps required for the performance of an individual audit should be settled in the relevant audit-related procedures, and the MAHs should ensure that audits are conducted in accordance with the written procedures.

9.8. Reporting

9.8.1. The findings of the auditors should be documented in an audit report and should be communicated to the Authority in a timely manner. The audit process should include mechanisms for communicating the audit

findings and receiving feedback and reporting the audit findings to the Authority.

9.8.2. Audit findings should be reported in line with their relative risk level and should be graded to indicate their relative criticality to risks impacting the Safety Monitoring System, processes and parts of processes. The grading system should be defined in the description of the quality management system for pharmacovigilance, and should take into consideration the thresholds noted below:

i. Critical is a fundamental weakness in one or more pharmacovigilance processes or practices that adversely affect the whole Safety Monitoring System and/or the rights, safety or well-being of patients, or that poses a potential risk to public health and/or represents a serious violation of applicable regulatory requirements.

ii. Major is a significant weakness in one or more pharmacovigilance processes or practices, or a fundamental weakness in part of one or more pharmacovigilance processes or practices that is detrimental to the whole process and/or could potentially adversely affect the rights, safety or well- being of patients and/or could potentially pose

a risk to public health and/or represents a violation of applicable regulatory requirements which is however not considered serious.

iii. Minor is a weakness in the part of one or more pharmacovigilance processes or practices that are not expected to adversely affect the whole Safety Monitoring System or process and/or the rights, safety or well-being of patients.

9.8.3. Issues that need to be urgently addressed should be communicated to the Authority as soon as possible but no later than 30 days.

9.9. Actions based on audit outcomes and follow-up of audits

9.9.1. Actions referenced in this section of the guideline, i.e., immediate action, prompt action, action within a reasonable timeframe, issues that need to be urgently addressed, or communicated in an expedited manner, are intended to convey timelines that are appropriate, relevant, and in line with the relative risk to the Safety Monitoring System. Corrective and preventive actions to address critical and major issues should be prioritised. The precise timeframe for action(s) related to a given critical finding, for example, may differ

depending on the nature of findings and the planned action(s).

9.9.2. The MAHs should be responsible for ensuring that a mechanism is in place to adequately address the issues arising from pharmacovigilance audits. Actions should include root cause analysis and impact analysis of identified audit findings and preparation of a corrective and preventive action plan.

9.9.3. The MAHs should ensure that effective action is implemented to address the audit findings. The implementation of agreed actions should be monitored in a systematic way, and the progress of implementation should be communicated on a periodic basis proportionate to the planned actions to the Authority. Evidence of completion of action should be recorded to document that issues raised during the audit have been addressed.

9.9.4. Capacity for follow-up audits should be foreseen in the audit programme. They should be carried out as deemed necessary, to verify the completion of agreed actions.

9.10. Quality Management System and record management practices

9.10.1. Competence of auditors and quality management of audit activities

i. Independence and objectivity of audit work and auditors

a) The MAHs should assign the specific responsibilities for the pharmacovigilance audit activities. Pharmacovigilance audit activities should be independent. The MAHs should ensure this independence and objectivity in a structured manner and document this.

b) Auditors should be free from interference in determining the scope of auditing, performing pharmacovigilance audits and communicating audit results. The main reporting line should be to the management with overall responsibility for operational and governance structure that allows the auditor(s) to fulfil their responsibilities and to provide independent, objective audit opinion.

c) Auditors can consult with technical experts, personnel involved in pharmacovigilance processes, and with the person responsible for pharmacovigilance; however, auditors should maintain an unbiased attitude that allows them to perform audit work in such a manner that they have an honest belief in their work product and that no significant quality compromises are made. Objectivity

requires auditors not to subordinate their judgement on audit matters to that of others.

ii. Qualifications, skills and experience of auditors and continuing professional development

a) Auditors should demonstrate and maintain proficiency in terms of the knowledge, skills and abilities required to effectively conduct and/or participate in pharmacovigilance audit activities. The proficiency of audit team members will have been gained through a combination of education, work experience and training and, as a team, should cover knowledge, skills and abilities in:

(i) Audit principles, procedures and techniques;

(ii) Applicable laws, regulations and other requirements relevant to pharmacovigilance;

(iii) Pharmacovigilance activities, processes and system(s);

(iv) Management system(s);

(v) Organisational system(s).

iii. Evaluation of the quality of audit activities

Evaluation of audit work can be undertaken by means of ongoing and periodic assessment of all audit activities, and self- assessment of audit activities (e.g. quality assurance of audit activities, compliance, audit programme, and audit procedures).

iv. Audits undertaken by outsourced audit service providers

Ultimate responsibility for the operation and effectiveness of the Safety Monitoring System resides within the MAHs. Where the MAH decides to use an outsourced audit service provider to implement the pharmacovigilance audit requirements based on these guidelines and perform pharmacovigilance audits:

a) The requirements and preparation of the audit risk assessment, the audit strategy and audit programme and individual engagements should be specified to the outsourced service providers, by the organisation, in writing;
b) The scope, objectives and procedural requirements for the audit should be specified to the outsourced service provider, by the organisation, in writing;

c) The organisation should obtain and document assurance of the independence and objectivity of outsourced service providers;

d) The outsourced audit service should also follow the relevant parts of these GVP guidelines.

v. Retention of audit reports

Retention of the audit report and evidence of completion of action needs to be in line with the requirements stipulated in these guidelines.

vi. Pharmacovigilance audit policy framework and organisational structure

9.10.2. Requirement to perform an audit

The MAH is required to perform regular risk-based audit(s) of their Safety Monitoring System, including audit(s) of its quality management system to ensure that it complies with the quality management system requirements. The dates and results of audits and follow-up audits should be documented.

9.10.3. The local Qualified Person responsible for Pharmacovigilance (LQPPV)

i. The local QPPV should receive pharmacovigilance audit reports and provide information to the auditors

relevant to the risk assessment, including knowledge of status of corrective and preventive actions.

ii. The local QPPV should be notified of any audit findings relevant to the Safety Monitoring System.

9.10.4. Requirements for audit reporting by the MAH

i. The MAH should place a note concerning critical and major audit findings of any audit relating to the Safety Monitoring System in the Safety Monitoring System Master File (PSMF). Based on the audit findings, the MAH should ensure that an appropriate plan detailing corrective and preventive action is prepared and implemented. Once the corrective and preventive actions have been fully implemented, the note may be removed. Objective evidence is required in order that any note of audit findings can be removed from the Safety Monitoring System Master File.

ii. The MAHs should ensure that a list of all scheduled and completed audits is kept in the annex to the Safety Monitoring System Master File. The dates and results of audits and follow-up audits should be documented.

9.10.5. Confidentiality

Documents and information collected by the internal auditor should be treated with appropriate confidentiality and discretion.

10. REFERENCES

1. NAFDAC *Good Pharmacovigilance Practice Guidelines*, 2021

2. European Medicines Agency (EMA). *Guideline on good pharmacovigilance practices (GVP): Module I – Pharmacovigilance systems and their quality systems.* EMA/119871/2012.

3. European Medicines Agency (EMA). *Guideline on good pharmacovigilance practices (GVP) – Module II (Rev 2) – Pharmacovigilance system master file (PSMF).* EMA/816573/2011 Rev 2

4. European Medicines Agency (EMA). Guideline on good pharmacovigilance practices (GVP) – Module III: Pharmacovigilance inspections (Rev. 2), 4 September 2026. EMA/119871/2012 Rev 2.

5. European Medicines Agency (EMA). Guideline on good pharmacovigilance practices (GVP) – Module IV: Pharmacovigilance audits (Rev. 1), 12 December 2012 (Last updated 11 August 2015). EMA/228028/2012 Rev 1.

6. European Medicines Agency (EMA). Guideline on good pharmacovigilance practices: Module V – Risk management systems (Rev. 2)

7. European Medicines Agency (EMA). Guideline on good pharmacovigilance practices (GVP) - Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev. 2)

8. European Medicines Agency (EMA). Guideline on good pharmacovigilance practices (GVP): Module VII – Periodic safety update report
9. European Medicines Agency (EMA). Guideline on good pharmacovigilance practices (GVP) - Module VIII – Post-authorisation safety studies (Rev. 3)
10. European Medicines Agency (EMA). Guideline on good pharmacovigilance practices: Module XV – Safety communication (Rev. 1)

11. Amendment Sheet

Date identified	Amendment identified by	Short description of the changes proposed to the document	Review of proposed amendment