Zambia Medicines Regulatory Authority

GUIDELINES ON SAFETY MONITORING OF MEDICINES AND ALLIED SUBSTANCES IN ZAMBIA

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i. Abbreviations

DHCP	Dear Healthcare Professional
DLP	Data Lock Point
DSUR	Development Safety Update Report
IBD	International Birth Date
LBD	Local Birth Date
MAH	Marketing Authorisation Holder
PASS	Post Authorisation Safety Study
PAES	Post Authorisation Efficacy Study
PV	Pharmacovigilance
PSUR	Periodic Safety Update Report
PBRER	Periodic Benefit Risk Evaluation Report
QPPV	Qualified person for Pharmacovigilance
RMP	Risk Management Plan
ZAMRA	Zambia Medicines Regulatory Authority

ii. Definitions

In this guideline, unless the context otherwise states:

"Adverse Event" means any untoward medical occurrence that may be present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of the product whether or not related to the product;

"Adverse Reaction" is a response to a medicinal product/product which is noxious and unintended. This includes adverse reactions arising from:

- The use of product within the terms of the marketing authorisation
- The use of product outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse and medication errors;
- Occupational exposure.

In this guideline, Adverse Drug Reaction (ADR), Adverse Reaction and adverse event are used interchangeably.

"Authority" means the Zambia Medicines Regulatory Authority;

"Dear Healthcare Professional Letter" is a correspondence usually in the form of a mass mailing from the Marketing Authorisation Holder (MAH), the local responsible person or the Authority addressed to doctors, pharmacists, nurses and other healthcare professionals regarding important new information;

"Identified risk" is an untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest.

"Local responsible person" has the meaning assigned to the words in the Medicines and Allied Substances (Marketing Authorisation of Medicines) Regulations, 2019;

"Local Birth Date" means the date of issue of marketing authorization in Zambia;

"Marketing Authorisation Holder" means a person to whom Marketing Authorization has been granted in accordance with section 39 of the Act;

"Medication Error" is an unintended failure in the treatment process with a medicine or an allied substance that leads to, or has the potential to lead to, harm to the patient;

"Medicinal Product" means any substance or combination of substances which may be administered to human beings in order to make a medical diagnosis or to restore, correct or modify the physiological functions in human beings, it includes nutritional supplements;

"New Chemical Entity" is a chemical or biologically Active Pharmaceutical Ingredient (API) that has not previously been registered as an ingredient of any pharmaceutical product;

"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" is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem;

"Post-Authorisation Efficacy Study" this study is performed after the marketing Authorisation and is aimed principally to further evaluate the efficacy of the medicinal product;

"Post-Authorisation Safety Study" is any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures;

"Potential Risk" is an untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed;

"Product" means medicines and allied substances;

"Qualified Person for Pharmacovigilance" means an individual resident in Zambia, employed and appointed by a Marketing Authorisation Holder as the person responsible for ensuring that the Marketing Authorisation Holder meets its obligations of monitoring the safety of products granted Marketing Authorisation;

"Risk Management Plan" is a detailed description of the risk management system. It includes information on a medicine's safety profile and explains the measures that are taken in order to prevent or minimize the risks of medicine in patients;

"Risk Management System" is a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimize risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions;

"Safety Concern" is an important identified risk, important potential risk or important missing safety information;

"Serious Adverse Drug Reaction or Adverse Event" is any untoward medical occurrence that at any dose:

- results in death;
- is life threatening - refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe-;
- requires inpatient hospitalisation or results in prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is a medically important event or reaction.

The term "**severe**" is often used to describe the intensity (severity) of a specific event. This is not the same as "**serious**," which is based on patient/event outcome or action criteria.

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

"Target Population" the patients who might be treated with the medicinal product in accordance with the indication(s) and contraindications in the authorised product information;

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

1. Introduction

This guideline on Safety Monitoring of Medicines and Allied Substances is issued by the Authority in pursuant to **Sections 47** and **68** of the Medicines and Allied Substances Act No.3 of 2013. The guideline defines the general norms and principles, set standards for continuous safety monitoring of medicines and allied substances granted Marketing Authorisation and, ensure that they continue to be safe for patients and the general public.

Medicines are approved based on clinical trials data available at the time of authorisation and in most cases on few volunteers. The limited number of participants included in clinical trials, the exclusion of certain patient groups, the limited duration of the clinical trials and the limitation of concomitant therapies do not allow a thorough evaluation of the safety profile. Under such circumstances, the detection or confirmation of rare adverse reactions is particularly difficult, if not impossible. This guideline therefore provides the requirements for safety monitoring during the life cycle of medicines and allied substances granted Marketing Authorisation and communication of safety information related to medicines and allied substances. Compliance with this guideline provides the public with assurance that the medicines and allied substances being made available on the Zambian market continue to meet the set standards of quality, safety and efficacy.

The Authority may rely on and use relevant decisions, reports or information from well-resourced regulatory authorities (or WHO-listed, Maturity level 3 or 4 Authorities) or from relevant regional and international bodies. That notwithstanding, it is equally important to note that the Authority may request information or material, or define conditions not specifically described in this Guideline or the Reliance guideline, to allow for adequate assessment of the safety, efficacy or quality of a medicine or allied substance. The Authority is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

The Authority may from time to time amend any part of this guideline.

Objective

This guideline sets out the general norms, principles and standards for continuous safety monitoring of medicines and allied substances on the Zambian market to ensure that their favorable benefit-risk balance is maintained for the protection of patients and the public.

Scope

This guideline provides safety monitoring requirements for all medicines and allied substances. It provides for monitoring and reporting of adverse reactions/events, medication errors, product quality defects and other safety issues as they may apply to medicines and allied substances. It applies to marketing authorisation holders, local responsible persons, qualified persons for safety monitoring, health professionals, patients/consumers and all persons involved in safety monitoring of medicines and allied substances. This guideline is intended to be applied during the period that a medicine or allied substance is marketed in Zambia.

2. Requirements for reporting adverse reactions/events, product quality problems and medication errors

This section contains requirements for reporting adverse reactions/events, product quality problems, medication errors, and any other medicine-related problem and includes:

a. Responsibilities,
b. Reportable events,
c. Required information,
d. Reporting format, and
e. Timelines.

2.1. Roles and responsibilities

2.1.1. Marketing Authorisation Holder

2.1.1.1. The Marketing Authorisation Holder (MAH), or their appointed Local Responsible Person (LRP), shall ensure that any medicine or allied substance made available on the Zambian market is safe for human or animal health when used under normal or reasonably foreseeable conditions of use, taking account of its presentation, packaging and labelling, instructions for use and disposal, and any other indications or promotional information they provide. Therefore, the MAH shall implement an appropriate safety monitoring system to monitor the safety of each medicine or allied substance they place on the market in Zambia.

2.1.1.2. For new chemical entities, in addition to spontaneous monitoring and reporting, the MAH shall put in place pharmacovigilance measures to actively monitor the safety of the product in clinical practice during the first five (5) years following grant of Marketing Authorisation. Passive surveillance will be required for the entire life-cycle of the product.

2.1.1.3. The Authority may also request the MAH to conduct formal post-authorisation safety studies, when necessary.

2.1.1.4. The Marketing Authorisation Holder shall employ, appoint and continuously have an appropriately qualified person responsible for pharmacovigilance resident in Zambia, referred to as the local qualified person for pharmacovigilance.

2.1.1.5. The local qualified person for pharmacovigilance (local QPPV) shall be a healthcare professional with experience/knowledge in all aspects of pharmacovigilance and may be a pharmacist or any other person with qualification in a health-related field with specialisation in pharmacovigilance. For the qualifications and responsibilities of the local Qualified Person for Pharmacovigilance, please refer to the guidelines for QPPV.

2.1.1.6. The Marketing Authorisation Holder shall communicate to the Authority any of the following information within 15 days of awareness:

i. Information that contradicts information already furnished to the Authority by the MAH or local responsible person;

ii. Information that indicates that the use of the registered product in accordance with the recommendations for its use may have an unintended harmful effect;

iii. Information that the registered product, when used in accordance with the recommendations for its use, may not be effective in relation to information submitted previously.

2.1.1.7. When the MAH is involved in partnerships, including those that are contractual, arrangements for meeting safety monitoring obligations shall be clearly specified in writing to the Authority. The Authority shall also be informed whenever there are amendments to the original contract with regards to the safety monitoring obligations.

2.1.1.8. When one product has different proprietary names and is registered separately or marketed by separate local responsible person or MAH the following shall apply:

i. Each MAH and local responsible person is obliged to meet the safety monitoring obligations for its brand of product(s).

ii. For products where co-marketing arrangements exist between the separate local responsible persons or MAH, joint safety monitoring data collection may be acceptable to the Authority only when it is duly informed of such arrangements.

iii. The MAH shall ensure that all information relevant to the risk-benefit balance of a registered product is reported promptly to the Authority.

2.1.1.9. Where the MAH or local qualified person for Pharmacovigilance receives a report of an adverse reaction from a patient/consumer, the patient/consumer should be advised to seek medical attention from a healthcare provider, when necessary.

2.1.2. The Healthcare Worker

2.1.2.1. Healthcare workers are encouraged to report all adverse reactions, product quality problems, medication errors and other product related problems detected or received from patients/consumers. The following will guide reporters on a general approach to patient/consumer reports:

i. Patients/consumers should be encouraged to report adverse reactions and seek medical attention through their healthcare providers.

ii. During all contacts, attempts should be made to obtain sufficient information to ascertain the nature and seriousness of the reaction.

2.1.2.2. Additional follow-up or medical confirmation may not be necessary for apparently non-serious and expected adverse reactions. On the other hand, if the reaction or event is serious /or unexpected, reasonable additional efforts should be made to contact the healthcare provider who attended to the patient/consumer or have the consumer provide the relevant medical documentation to allow for assessment of causality by the Authority.

2.1.3. The Patient/Consumer

2.1.3.1. Patients/Consumers are encouraged to report all adverse reactions, product quality problems, medication errors or other medicine related problems to their healthcare providers. All patient/consumer reports will however be documented as any other type of report and will be considered when overall safety assessments are made.

2.1.3.2. The patients/consumers may also report adverse reactions directly to the Authority using channels provided in **Appendix Id – Electronic reporting platforms**

2.1.4. The Authority

2.1.4.1. The Authority shall continually monitor the safety of the products regulated by it, through analysis of the adverse reaction and adverse event reports and take appropriate regulatory action, when necessary.

2.1.4.2. The Authority shall set up a Technical Committee of experts to provide expert advice and recommendations to the Authority on matters relating to the safety of products. Its functions include:

i. Causality assessment of adverse reaction or adverse event reports presented to the Committee by the Authority;
ii. Evaluation of post-approval product safety, quality, efficacy and effectiveness issues. Such evaluation will be based on the information provided to the Technical Committee by the Authority. Evaluations will be relevant to the risk/benefit implications for the use of the product in question;
iii. Upon request, the Technical Committee will make recommendations to the Authority regarding actions the Authority may take to resolve issues or concerns related to post-approval product safety;
iv. The Technical Committee may also recommend publication of case reports, their risk/benefit evaluations; recommendations and communications arising from the Technical Committee meetings that are deemed appropriate for medical and scientific journals; and
v. Advise the Authority about the safety of registered products.

2.1.4.3. The membership of the Technical Committee shall include external experts from various relevant areas of expertise.

2.2. Reporting adverse reactions/events, product quality problems and medication errors

2.2.1. For all medicines and allied substances, the following should be reported:

2.2.1.1. Adverse reactions/events resulting from medicines, vaccines and other biological products, nutritional (food) supplements, medical devices, cosmetics, antiseptics and disinfectants.

2.2.1.2. Adverse reactions/events resulting from the following special situations:

i. Use of a medicine or allied substance in children,
ii. Use of a medicine or allied substance in pregnant or lactating women,

iii. Use of a medicine or allied substance in drug abuse, drug misuse and drug overdose,

iv. Drug interactions,

v. Suspected substandard or falsified medicines, and

vi. Medication or use errors.

2.2.1.3. Medication or use errors, whether or not an adverse reaction/event occurred.

2.2.1.4. Product quality problems (i.e. poor packaging, questionable stability, suspected contamination, substandard and falsified medicines, and lack of therapeutic efficacy).

Note: *More details on specific safety monitoring areas will be provided in specific guidelines including guidelines on vaccine safety surveillance, heamovigilance guidelines, materiovigilance guidelines and cosmetovigilance guidelines.*

2.2.2. Key information to be provided on the reporting Form

2.2.2.1. Patient information

i. In reports of adverse reactions/events where a patient or user of a medicine was harmed, information that can help identify the patient or user shall be provided. However, in some cases, patient or user personal identifying information may not be required. The following are examples of details to be provided:

   a. Patient initials (locator information such as name, address and contact information may be needed if reporting an adverse event following immunisation),

   b. Institutional or hospital identification marks such as file numbers, patient number, codes, etc,

   c. Date of birth (age or age group where the date of birth is not known),

   d. Sex (male or female),

   e. Information on pregnancy and lactation as applicable for women of childbearing potential,

   f. Other patient factors that can help with clinical assessment of the case such as, weight and height.

ii. The above may not be applicable for certain reports including product quality problems or medications errors where a patient was not involved or harmed.

2.2.2.2. Information on the problem

i. Adverse reaction/event

a. Description of the adverse reaction/event including signs and symptoms, impression/diagnosis,
b. Date (and time as applicable) of onset,
c. Date (and time as applicable) of resolution (if applicable),
d. Other information on the outcome such as not recovered or unknown,
e. Seriousness of the adverse reaction/event (if the reaction resulted in death, was life threatening, caused or prolonged hospitalization, was a congenital anomaly/birth defect, or other medically important condition),
f. Relevant medical history, medicines or allied substances taken or used in the recent past, including traditional medicines and their period of exposure,
g. Other patient conditions relevant to the case, and
h. Laboratory results and other tests or investigations relevant to the case.

ii. Medication or use error (including near misses)

a. Description of the error, incident or near miss and how it was identified,
b. Date (and time as applicable) of occurrence or discovery as applicable,
c. Measures proposed or implemented to avoid recurrence including proposed mechanisms for monitoring implementation of these measures.

iii. Product quality problem

a. Description of the problem, and
b. Description of the immediate action taken to prevent harm.

iv. Other safety issue

a. Description of the safety issue, and
b. Description of the immediate action taken to prevent harm, where applicable.

2.2.2.3. Information on medicine or allied substance

i. Suspected medicine or allied substance

a. Name of the medicine or allied substance (trade/brand and generic/common name),

b. Formulation, strength, pack type and pack size,

c. Marketing Authorisation number, batch/lot number, expiry date (for medical devices: catalogue/model/serial number),

d. Reason (indication) why the medicine or allied substance was used,

e. How the medicine or allied substance was used (e.g. dosage and route of administration),

f. Dates (and time as applicable) when the medicine or allied substance was used,

g. Name and address of the manufacturer, and

h. Name and address of the supplier (distributer, retailer, dispenser, etc, where available attach supply documents such as receipt, delivery note, invoice etc).

Note: *details of the manufacturer and supplier are mandatory for product quality problems.*

ii. Concomitant medicines and allied substances

a. Name of the medicine or allied substance (trade/brand and generic/common name),

b. Reason (indication) why the medicine or allied substance was used,

c. How the medicine or allied substance was used (e.g. dosage and route of administration), and

d. Dates (and time as applicable) when the medicine or allied substance was used.

2.2.2.4. Details of the Reporter

i. Name of reporter;
ii. Profession of reporter;
iii. Institution/facility;
iv. Signature and date as applicable;
v. Contact details of reporter (phone number, e-mail address and/or postal address) should be provided to enable the National Pharmacovigilance Unit to provide feedback on the report submitted or contact the reporter for follow up information, when needed.

2.2.2.5. The minimum information for valid safety report for an adverse reaction /event should include at least:

i. One identifiable patient - any one of several data elements is considered sufficient to define an identifiable patient (e.g. Initials, age, sex);
ii. One identifiable reporter - any one of several data elements is considered sufficient to define an identifiable reporter (e.g. Initials, address, qualifications);
iii. One adverse event/reaction (or outcome); and
iv. One suspected or interacting drug.

2.2.2.6. The minimum information for valid safety report for an medication error, product quality problem or other safety issue other than an adverse reaction/event should include at least:

i. One identifiable reporter - any one of several data elements is considered sufficient to define an identifiable reporter (e.g. Initials, address, qualifications);
ii. One identified safety issue/problem/error; and
iii. One suspected or interacting drug.

Note: *Additional validation rules for the required 'minimal information' might apply depending on the system used for reporting or other criteria as may be advised by the Authority.*

2.2.2.7. Additional information, not available at the time of the initial report, should be provided in the form of follow-up reports.

2.2.2.8. Separate sheets may be attached in cases where there is more than one suspected product or for any extra information.

2.2.2.9. Samples the reporter or other responsible person should return a sample of a suspected medicine or allied substance in the container or package in which the medicine or allied substance was (as applicable) when the quality problem was identified. Additional samples of the unopened suspected medicine or allied substance will be required for quality testing at the laboratory. Samples should be stored, as far as possible, within their original packaging and under the applicable storage conditions.

2.2.3. How to Report

2.2.3.1. To report a suspected adverse reaction/event, product quality problem, medication/use error or other safety issue/problem for medicines or allied substances marketed in Zambia, reporters should complete a copy of the Reporting Form (Appendix I - Reporting Forms).

2.2.3.2. Paper form may be obtained from the National Pharmacovigilance Unit (NPVU) at the Authority's Head Office or regional or sub-regional offices of the Authority or (contact details provided in Appendix Id – Contact information for reporting) or health facilities or downloaded from the Authority's website.

2.2.3.3. The completed report may be delivered to the NPVU at the Authority's Head Office in Lusaka. A scanned copy of the completed report can be sent to the Authority by email or WhatsApp (Appendix Id – Contact information for reporting).

2.2.3.4. A copy of the report should be shared with and maintained by the respective focal person at facility, district, provincial or national levels for health facilities and where applicable by the Local QPPV at the local responsible person/MAH's designated place.

2.2.3.5. Electronic reporting tools are available for reporting by healthcare professionals and patients/consumers. These tools are published on the Authority's website (Appendix Id – Electronic reporting platforms).

2.2.4. Confidentiality of Adverse Reaction Reports

2.2.4.1. Any information related to the reporter and patient must be kept strictly confidential and only used for purposes of reporting to the Authority.

2.2.5. Follow-Up Information Reported Adverse Reaction

2.2.5.1. Any follow-up information for a report that has already been submitted can be sent on another form or on a supplementary sheet. This can also be communicated by telephone or e-mail, if convenient. To match this information with the original report, the reporter should indicate that it is follow-up information and provide the date of the original report or the report case number, if known. It is very important that follow up reports are identified and linked to the original report.

2.2.6. Duplication of Report

2.2.6.1. If the MAH or qualified person for Pharmacovigilance is aware that a person has reported a reaction of one of their products directly to the Authority, the MAH or qualified person for Pharmacovigilance should still report the adverse reaction informing the Authority that the report is a duplicate of a previous report. In such a situation, the MAH or qualified person for Pharmacovigilance shall provide all the available details making appropriate references to the information provided by the initial reporter, in order to aid identification of the duplicate.

2.2.7. Reporting format and details to be submitted in the report

2.2.7.1. Adverse reactions/events, product quality problems and medication errors shall be considered reportable according to the requirements outlined in these guidelines regardless of whether or not the product was used in accordance with the approved Product Information.

2.2.7.2. Reporting can be done using the reporting form which can be obtained from the Authority (Appendix I - Reporting Forms). Marketing Authorisation Holders may use their in-house reporting forms, provided all the necessary data elements are included on the forms in a readable, searchable format and the form complies with the CIOMS I format.

2.2.7.3. All electronic reporting systems for reporting adverse reactions/events should be ICH E2B compliant.

2.2.8. Reporting by Local QPPV

2.2.8.1. The Local QPPV shall submit all relevant information available at the time of initial notification of an adverse reaction. Details including but not limited to post-mortem reports and relevant laboratory data may be attached when necessary.

2.2.8.2. The original words/description (verbatim) used by the initial reporter to describe the adverse reaction should be provided. The product (generic and/or trade) name must be provided as reported by the initial reporter. Additional information, not available at the time of initial report, should be provided in the form of follow-up reports.

2.2.8.3. The local QPPV is required to submit the name or initials, address and telephone number and profession of the initial reporter on the adverse reaction report form.

2.2.9. Reporting Timelines

2.2.9.1. Healthcare workers

i. All serious suspected and serious, unexpected adverse reactions/events, serious medication errors and class I and II product quality problems associated with the use of a product in Zambia should be reported to the Authority as soon as possible but within 7 days of becoming aware of an event with a fetal outcome and within 15 days of becoming aware of a serious event without a fetal outcome.

ii. Non-serious adverse reactions, medication errors and class III product quality problems should be reported to the Authority as soon as possible but not later than 30 days.

iii. For a summary of reporting timelines in **Appendix IIa: Reporting Timelines**.

2.2.9.2. MAH/Local responsible person

i. Serious adverse reaction reports, medication error reports and class I and II product quality problem reports received by the MAH or local responsible person shall be submitted to the Authority within 7 days of becoming aware of an event with a fetal outcome and within 15 days of becoming aware of a serious event without a fetal outcome.

ii. In case all the information needed is not available, the Marketing Authorisation Holder or local responsible person should submit an initial report containing at least the minimum data elements required (i.e. patient details, suspected product details, reaction details and the reporter details) in order to meet the expedited reporting time frame.

iii. A follow-up report containing more detailed information should be submitted as soon as this becomes available but not more than 15 days from date of initial report.

iv. Non-serious adverse reactions, medication errors and class III product quality problem reports should be submitted to the Authority as soon as possible but not later than 30 days.

v. The MAH/local responsible person is required to search widely referenced databases (e.g., Medline, Embase) on a regular basis and submit any case originating from Zambia on registered products to the Authority.

vi. The MAH/local responsible person is also required to search local scientific and medical journals not included in widely referenced databases on scheduled basis depending on the periodicity of such journals and submit any publication identified as coming from Zambia on marketed products to the Authority. References to publications should be accompanied by a link to the article. If the article describes identifiable patients, adverse reaction report(s) should be completed for each patient and the publication authors considered as the primary source.

vii. Reports from lay press should be handled as spontaneous report and every attempt should be made to collect minimum information that constitutes a valid case report.

viii. Internet or digital media under the management of the MAH/local responsible person should be screened regularly for adverse reaction reports and reports submitted to the Authority within the specified timelines.

ix. Where the MAH/local responsible person becomes aware of reports from non-company sponsored internet sites or social media, the MAH/local responsible person should assess the report to determine whether minimum reporting criteria are met. These reports should also be treated as spontaneous reports.

x. All safety information that becomes available to the MAH/local responsible person as a result of follow-up activities should also be reported within 30 days.

xi. All Suspected Unexpected Serious Adverse Reactions (SUSARs) and other serious reactions occurring in all post authorisation safety studies within or outside Zambia, which the MAH/local responsible person is undertaking or aware of, should be reported within 7 days of an event with a fetal outcome and within 15 days of becoming aware of a serious event without a fetal outcome. However, if the post-authorisation safety study is conducted by an investigator independent of the MAH/local responsible person (e.g. "investigator –initiated post authorisation safety study"), the responsibility for reporting adverse reactions to the Authority shall rest with the investigator and not the MAH/local responsible person.

xii. Significant safety issues identified by the MAH/local responsible person as a result of ongoing review and analysis of all information (including foreign adverse reaction reports) that has a potential major impact on the benefit-risk assessment of the product or immediate safety action taken by a foreign regulatory agency, including the basis for such actions shall be reported to the Authority within 15 days of awareness.

xiii. Foreign regulatory agency decisions to be communicated to the Authority may include any matter relating to:

a. The safety of the medicine or allied substance,
b. Withdrawal or suspension of availability of the medicine or allied substance,
c. The addition of a contraindication or the modification for safety reasons of an existing contraindication, and

d. Warning or precaution statement in the approved product information.

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

xv. MAH/Local responsible person of both innovator and generic drugs are required to submit PSUR/PBRER to the Authority at stipulated timelines (Section 3.1).

2.2.10. Other Sources of Reports

2.2.10.1. Reports from non-medical sources (lay press) should be handled by local responsible person/MAHs as spontaneous reports. Every attempt should be made to follow-up the case to obtain the minimum information that constitutes a valid case report.

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

2.2.11. Reporting in Special Situations

2.2.11.1. Lack of Efficacy: Every case of lack of efficacy should be reported to the Authority using the reporting forms that are available in health facilities or electronic platforms provided in Appendix I - Reporting Forms. Reports of lack of efficacy should be considered serious and reported within 7 days of becoming aware of a case with a fetal outcome and within 15 days of become aware of a case without fetal outcome.

2.2.11.2. Overdosage, occupational exposure, exposure in pregnancy and breastfeeding

i. If not associated adverse reactions/events, these reports should not be reported as adverse reactions/events.

ii. Overdose should be reported to the Authority as medication errors.

iii. Cases of occupational exposure and exposure in pregnancy and breastfeeding should be treated on a case by case depending on the risks of the medicine or allied substance or the risk management plan and followed up as applicable to document the outcome. Where the outcome constitutes an adverse reaction/event, an individual case safety report should be generated and submitted to the Authority.

2.3. Feedback on Reports Received

2.3.1. Adverse reaction/event reports

2.3.1.1. The Authority shall acknowledge receipt of the adverse reaction report within 15 days of receipt. The acknowledgement shall be by phone or e-mail.

2.3.1.2. The feedback on causality assessment of the adverse reaction reports shall be communicated to the reporter within 30 days of such evaluation being undertaken by the Authority.

2.3.1.3. The Authority may investigate or direct the MAH or Local Responsible Person (or QPPV), or a public health program or other person responsible, to investigate cases of serious adverse events or a cluster of adverse events or product quality problems.

2.3.2. Quality Problem Reports

2.3.2.1. The Authority shall acknowledge receipt of the product quality problem report within 15 days of receipt. The acknowledgement shall be by phone or e-mail.

2.3.2.2. The feedback on quality analysis or evaluation of the reported products shall be communicated to the reporter within 30 days of such analysis or evaluation being undertaken.

2.3.3. Risk Management Plans, PSURs (or PBRERs)

2.3.3.1. The Authority shall acknowledge receipt and communicate preliminary evaluation comments to the Marketing Authorisation Holder within 30 days of receipt of the report.

3. Requirements for periodic reports, risk management plans, post-authorisation studies, safety variations and safety communication

This section contains the requirements for post-approval safety monitoring of medicines and allied substances granted Marketing Authorisation, including requirements for the following:

a. Periodic Safety Update Reports (PSUR) or Periodic Benefit-Risk Evaluation Reports (PBRER)
b. Development Safety Update Reports (DSUR)
c. Risk Management Plan (RMP)
d. Post Authorisation Safety Studies (PASS)
e. Post Authorisation Efficacy Studies (PAES)
f. Safety Variations
g. Safety Communication

3.1. Periodic Safety Update Reports or Periodic Benefit-Risk Evaluation Reports

3.1.1. Requirement to submit Periodic Safety Update Reports (PSUR) or Periodic Benefit-Risk Evaluation Reports (PBRER)

3.1.1.1. PSURs/PBRERs will be submitted only for medicinal products granted Marketing Authorisation in Zambia.

3.1.1.2. The main objective of a PSUR is to present a comprehensive, concise and critical analysis of the benefit-risk balance of the medicinal product considering new or emerging information in the context of cumulative information on benefits and risks. The PSUR is a tool for post-authorisation evaluation at defined time points in the life-cycle of a product.

3.1.1.3. The PBRER is aimed at presenting a comprehensive and critical analysis of new or emerging information on the risks of the medicinal product, and, where pertinent, on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile.

3.1.1.4. PSURs/PBRERs will not be requested routinely for generic medicinal products, herbal medicines and allied substances. Under these conditions, the PSUR/PBRER will be submitted only when requested by the Authority based on safety concerns and/or at renewal of Marketing Authorisation.

Note: *While PSUR and PBRER may be used interchangeably in this guideline, it must be understood that these documents are different. Whilst the primary objective of the PSUR is to provide a comprehensive picture of the safety of approved medicinal products with recognition that the assessment of the risk of a medicinal product is most meaningful when considered in light of its benefits, the PBRER provides a greater emphasis on benefit than the PSUR, particularly when risk estimates change importantly.*

For additional information on the differences between the PSUR and PBRER, reference is made to ICH E2C and ICH E2C (R2) Guidelines, respectively.

3.1.2. Objectives of PSUR/PBRER

3.1.2.1. PSUR/PBRER presents the worldwide safety experience of a medicinal product at defined times post-authorisation, to:

i. Report all the relevant new information from appropriate sources;
ii. Relate these data to patient exposure;
iii. Summarize the market authorisation status in different countries and any significant variations related to safety;
iv. Create the opportunity for an overall safety re-evaluation;
v. Provide a formal and concise evaluation of benefit, unless the safety or benefit-risk profile has changed significantly during the reporting interval.
vi. Indicate whether changes should be made to product information to optimize the use of the medicine or allied substance.

3.1.3. Frequency and Format of Submission

3.1.3.1. For New Chemical Entities (NCEs), PSURs/PBRERs shall be submitted as stated below, unless otherwise requested by the Authority.

i. Six (6) monthly for the first two (2) years;
ii. Thereafter, annually for the subsequent three (3) years;
iii. At the time of renewal of Marketing Authorisation of the product; and
iv. Upon request by the Authority.

3.1.3.2. For all other medicines and allied substances, the most recent PSUR/PBRER should be submitted upon request and/or at the time of renewal of Marketing Authorisation of the product.

3.1.3.3. PSURs and PBRERs should be harmonised with the International Birth Date (IBD) of the medicine or allied substance.

3.1.3.4. Each PSUR and PBRER should cover the period of time since the last PSUR/PBRER and should be submitted within 70 calendar days after the Data Lock Point (DLP) for the PSUR/PBRER covering intervals of up to 12 months and within 90 calendar days for the PSUR/PBRER covering intervals in excess of 12 months. The day of DLP is day 0 of the 70- or 90-calendar day interval between the DLP and report submission.

3.1.3.5. Presentation of the information contained in the PSUR and PBRER shall be in the format recommended by ICH E2C and ICH E2C R2 Guidelines, respectively.

3.1.3.6. For medicinal products with Marketing Authorisation in different countries, the MAH may synchronize the Local Birth Date (LBD) with the IBD. The Authority will accept a single harmonised IBD and DLP for each product to reduce the burden of work in preparing PSURs/PBRERs for different regulatory authorities.

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

3.1.3.8. 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 a medicinal product.

3.2. Development Safety Update Reports

3.2.1. Marketing Authorisation Holders, Sponsors and Investigators in clinical trials are required, to submit to the Authority, periodic Development Safety Update Reports (DSUR) on medicines and allied substances granted Authorisation that are under further study.

3.2.2. DSUR should provide safety information from all ongoing clinical trials and other studies that are ongoing or completed during the review period, including:

3.2.2.1. Clinical trials using an investigational drug such as human pharmacology, therapeutic exploratory and therapeutic confirmatory trials (Phase I to III);

3.2.2.2. Clinical trials conducted using marketed drugs in approved indications such as therapeutic use trials (Phase IV);

3.2.2.3. Therapeutic use of an investigational drug;

3.2.2.4. Clinical trials conducted to support changes in the manufacturing process of medicinal products; and

3.2.2.5. Any significant other findings pertinent to the safety of the investigational drug.

3.2.3. The DSUR should be submitted to all concerned regulatory authorities no later than 60 calendar days after the DSUR data lock point.

3.3. Risk Management Plan

3.3.1. Risk Management Plans (RMPs) include information on a medicine's safety profile and explain the measures that are taken to prevent or minimise the medicine's risks in patients, post-authorisation. The RMP details the known safety concerns with the medicine and how they can be managed. It also includes details of any additional studies that have been recommended at the time of licensing to provide more information on the medicine's safety profile.

3.3.2. In relation to medical devices, a Risk Management Plan that complies with ISO 14971 (the international standard for medical device risk management) will be acceptable.

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

3.3.3.1. Ensuring that it constantly monitors the risks of its medicines and allied substances issued with Marketing Authorisation in Zambia in compliance with relevant legislation and reports the results of this, as required, to the Authority;

3.3.3.2. Taking all appropriate actions to minimise the risks of the medicine or allied substance and maximise the benefits;

3.3.3.3. Ensuring the accuracy of all information in relation to its medicines and allied substances, and actively updating and promptly communicating it when new information becomes available.

3.3.4. Objectives of a Risk Management Plan (RMP)

3.3.4.1. The overall aim of risk management is to ensure that the benefits of a particular medicine or allied substance exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole.

3.3.4.2. The RMP must contain the following elements:

i. Identify or characterise the safety profile of the medicine or allied substance concerned;

ii. Indicate how to characterise further the safety profile of the medicine or allied substance concerned;

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

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

v. Describe what is known and not known about the safety profile of the concerned medicine or allied substance;

vi. Indicate the level of certainty that efficacy shown in clinical trial populations will be seen when the medicine or allied substance is used in the wider target populations seen in everyday medical practice;

vii. Document the need for studies on efficacy in the post-authorisation phase (also known as effectiveness studies); and

viii. Include a description of how the effectiveness of risk minimisation measures will be assessed.

3.3.5. When to submit a Risk Management Plan (RMP)

3.3.5.1. An RMP should be submitted as part of an application for Marketing Authorisation as stated below.

3.3.5.2. A Risk Management Plan should be submitted:

i. With an application for any product containing a New Chemical Entity.

ii. With an application for a new dosage form or route of administration for a generic medicine or allied substance.

iii. With an application for a biosimilar medicine.

iv. With an application for pediatric use marketing authorisation.

v. With an application involving a significant change in marketing approval (for example: new manufacturing process of a biotechnologically-derived product, significant change in indication, including a new pediatric indication) unless it has been agreed with the Authority that submission of RMP is not required.

vi. With an application for a generic medicine or allied substance where the reference product has an RMP and a safety concern requiring additional risk minimisation activities has been identified with the reference medicine or allied substance.

vii. With an application for new fixed-dose combination applications irrespective of how long any of the ingredient(s) in the combination has been used as a single agent.

viii. For generic medicine or allied substance, where the changes compared with the reference medicine or allied substance suggest different risks.

ix. On the request of the Authority (both pre-and post-authorisation).

x. On the initiative of MAH when they identify a safety concern with a medicine or allied substance at any stage of its life cycle.

3.3.5.3. An update, as applicable, shall be submitted at any time during a product's life-cycle and when requested by the Authority.

3.3.6. Structure of the RMP

3.3.6.1. The RMP consists of seven parts as listed below; certain parts specifically the safety specification is subdivided into modules so the content can be tailored to the specifics of the medicinal product and modules added/removed or re-used in other documents (e.g. PSURs). RMP part II modules generally follow the section titles in the Safety Specification of ICH-E2E, whilst RMP part III follows the Pharmacovigilance Plan.

Part I: Product(s) overview

Part II: Safety specification

Module SI: Epidemiology of the indication(s) and target population(s)

Module SII: Non-clinical part of the safety specification

Module SIII: Clinical trial exposure

Module SIV: Populations not studied in clinical trials

Module SV : Post-Authorisation experience

Module SVI: Additional requirements for safety specification not discussed in ICH-E2E (e.g. off label use, misuse and abuse, transmission of infectious disease, medication error)

Module SVII: Identified and potential risks

Module SVIII: Summary of the safety concerns

Part III: Pharmacovigilance plan

Part IV: Plans for post-authorisation efficacy studies

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimisation measures)

Part VI: Summary of the risk management plan

Part VII: Annexes

3.3.6.2. For detailed description of each part of the RMP and the format acceptable to the Authority, refer to guidelines on Good Pharmacovigilance Practices (GVP) in Zambia and European Medicines Agency GVP Module V – Risk management systems.

3.3.6.3. If the RMP is submitted as part of the Marketing Authorisation application, cross references to other parts of the dossier should be avoided since it is intended that the RMP should be a stand-alone document.

3.3.7. Zambia Specific Annex to the Global or EU-RMP

3.3.7.1. Where an existing global or EU RMP is submitted, a Zambia Specific Annex shall be included to the Global or EU RMP. A Zambia Specific Annex is required to show adapt the implementation of the RMP to the Zambian set up.

3.3.7.2. The Zambia Specific Annex shall 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.

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

3.3.8. Content of Zambia Specific Annex

3.3.8.1. The Annex shall include differences in indications between the Global/European Union (EU) and Zambia if applicable.

3.3.8.2. The Annex shall discuss 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).

3.3.8.3. The Annex shall include information on potential for medication errors or other risks in the Zambian setup.

3.3.8.4. The Annex shall discuss the applicability of Global/EU activities to the Zambian environment if no Zambia specific activities are planned.

3.3.9. Format of Zambia Specific Annex

3.3.9.1. The Zambia Specific Annex shall be the format described below.

xi. *Introduction* - Purpose of Zambia Specific Annex

xii. *Pharmacovigilance practice* - Routine pharmacovigilance systems in Zambia and studies referenced in the RMP. Description of involvement of Zambia and applicability of global studies to the Zambian environment, or a justification if not applicable or relevant to the Zambian environment.

xiii. *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.

xiv. Provide a justification if activities in the Global/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.

xv. *Contact person for RMP* - This is the person the MAH considers responsible for the implementation of the RMP activities in Zambia and shall be the local QPPV.

3.4. Post-Authorisation Safety Study

3.4.1. A Post-Authorisation Safety Study (PASS) may be initiated and managed by the MAH. A PASS may be conducted by a third party on behalf of the MAH. The Authority may request the MAH to conduct a PASS as a condition for grant of Marketing Authorisation. The guidance should be used for all PASS.

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

3.4.3. Objectives of PASS

3.4.3.1. A PASS is conducted with the following objectives:

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

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

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

iv. Measure the effectiveness of a risk minimisation activity;

v. evaluate the risks of a medicinal product after long-term use; and

vi. Provide evidence about the absence of risks.

3.4.4. When to conduct a PASS

3.4.4.1. A PASS may be requested by the Authority and conducted by local responsible persons or MAHs under the following conditions:

i. As a condition to the granting of the marketing authorisation, or after the granting of a marketing authorisation if there are concerns about the risks of the authorized medicinal product.

ii. Required in the risk management plan to investigate safety concerns or evaluate the effectiveness of risk minimisation activities.

iii. PASS conducted voluntarily by the MAH or local responsible person.

3.4.4.2. The study protocol for post-authorisation studies shall be approved by a Research Ethics Committee.

3.4.4.3. The intention to conduct a post authorisation study shall be notified to the Authority.

3.4.4.4. The notification to the Authority shall be accompanied by cover letter, study protocol and ethics approval.

3.4.4.5. For investigator-initiated PASS, the notification to the Authority shall be accompanied by cover letter, study protocol, ethics approval and a written documentation to show support from the Local QPPV, local responsible person or MAH.

3.4.4.6. The Authority shall issue a no objection letter upon satisfactory review of the protocol.

3.4.5. Study population

3.4.5.1. The study should be conducted in a Zambian population resident in Zambia or in a study population to be determined in consultation with the Authority.

3.4.6. Study Design

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

3.4.7. Roles and Responsibilities

3.4.7.1. Local responsible person or Marketing Authorisation Holder (MAH) shall:

i. Bear sole responsibility for all regulatory and technical aspects of the PASS.
ii. Appoint a Principal Investigator.
iii. Develop the study protocol following the format provided in section 3.4.8.
iv. Ensure that the PASS does not commence before necessary authorisations are obtained.

v. Ensure the study is conducted in compliance with the approved protocol, good practices and applicable regulatory requirements.

vi. Ensure the final study report is submitted to the Authority not later than 12 months after the end of data collection.

3.4.7.2. Local QPPV

i. Submit notification for intention to conduct a PASS to the Authority by submitting a cover letter and protocol.

ii. Submit Individual Cases Safety Reports reported in the study to the Authority.

iii. Submit other safety reports and updates to the Authority.

iv. Submit a final study report to the Authority.

3.4.7.3. The Authority

i. A PASS in form of a clinical trial shall be approved in accordance with clinical trial guidelines.

ii. The Authority shall within, 60 calendar days, issue the applicant with a no objection letter if the submission meets the following conditions:

a. The PASS is not an interventional study or clinical trial.

b. Ethics approval has been obtained from an accredited ethics committee.

c. The arrangements in the study protocol including objectives, methods and reporting are appropriate, and

d. The study does not abrogate any other written law.

3.4.8. Study Protocol

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

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

iii. Marketing authorisation holder: name and address of the marketing authorisation holder.

iv. 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. A list of all collaborating institutions and investigators should be made available to the Authority.

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

vi. 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.

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

viii. 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.

ix. 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.

x. Research methods: description of the research methods, including:
   a. Study design: overall research design and rationale for this choice.
   b. Setting: study population defined in terms of persons, place, time period, and selection criteria, including the rationale for any inclusion and exclusion criteria and their impact on the number of subjects available for analysis. Where any sampling from a source population is undertaken, description of the source population and details of sampling methods should be provided. Where the study design is a systematic review or a meta-analysis, the criteria for the selection and eligibility of studies should be explained.
   c. 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.
   d. Data sources: strategies and data sources for determining exposures, outcomes and all other variables relevant to the study objectives, such as potential confounding variables and effect modifiers. Where the study will use an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data should be reported. If data collection methods or instruments are tested in a pilot study, plans for the pilot study should be presented. If a pilot study has already been performed, a summary of the results should be reported. Involvement of any expert committees to validate diagnoses should be stated. In case of a systematic review or meta-analysis, the search strategy and processes and any methods for confirming data from investigators should be described.
   e. Study size: any projected study size, precision sought for study estimates and any calculation of the sample size that can minimally detect a pre-specified risk with a pre-specified statistical precision.
   f. Data management: data management and statistical programmes to be used in the study, including procedures for data collection, retrieval and preparation.

g. 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.

h. Quality control: description of any mechanisms and procedures to ensure data quality and integrity, including accuracy and legibility of collected data and original documents, extent of source data verification and validation of endpoints, storage of records and archiving of statistical programmes. As appropriate, certification and/or qualifications of any supporting laboratory or research groups should be included.

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

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

k. 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.

l. Plans for disseminating and communicating study results, including any plans for submission of progress reports and final reports.

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

3.4.9. Amendments

3.4.9.1. Any amendment to the PASS protocol and study arrangements shall be submitted to the Ethics Committee(s) that originally approved the protocol and the Authority, in the case of clinical trials, for approval before such amendments are carried out.

3.4.10. Reporting Vigilance Data to the Authority

3.4.10.1. Data relevant to the risk-benefit balance of the product

The Local responsible person or MAH shall monitor the data generated while the study is being conducted and consider their implications for the benefit-risk balance of the medicinal product concerned. Any new information that may affect the benefit-risk balance of the medicinal product should be communicated immediately by email to the Authority and followed up by an official letter within 15 days to the Director General. Information affecting the risk-benefit balance of the medicinal product may include that arising from an analysis of adverse reactions and aggregated data. This communication should not affect information on the results of studies which should be provided by means of PSURs or PBRER and in RMP updates, where applicable.

3.4.11. Reporting of adverse reactions/adverse events

3.4.11.1. Adverse reactions/adverse events should be reported to Authority. Procedures for the collection, management (including a review by local responsible person or the MAH if appropriate) and reporting of suspected adverse reactions/adverse events should be put in place and summarised in the study protocol.

3.4.11.2. Reporting can be done using the adverse reaction reporting form which can be obtained from the Authority's office or applicants may use their in-house reporting forms, provided all the necessary data elements are included on the forms in a readable format and the form also complies with the CIOMS 1 format (Refer to ZAMRA Guidelines for reporting adverse reactions).

3.4.12. Study reports

3.4.12.1. Progress Report

i. The progress report should be submitted in the format approved by the Authority. Refer to clinical trial guidelines.

ii. If a study is discontinued, the Local QPPV, MAH or local responsible person should inform the Authority with reasons for the termination within 30 days of termination of the study.

3.4.12.2. Final Report

i. The final study report should be submitted to the Authority no later than 12 months after 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.

ii. The final study report should contain information in the format prescribed in the Guideline on Good Vigilance Practices (GVP), Module VIII – Post-Authorisation Safety Studies.

iii. Where the result of the PASS affects the risk management system or the marketing authorisation status of the medicinal product, this shall be communicated to the Authority and steps to incorporate these changes in the RMP and variation to the marketing authorisation described.

iv. The Authority may also request variation to the risk management system or the marketing Authorisation after review of the PASS report.

3.5. Post-Authorisation Efficacy Study

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

3.5.2. The Authority may request such studies when there are important questions about the efficacy of the medicine that can only be answered once the product is in general use, or when questions arise in the post-authorisation period.

3.5.3. When a PAES may be conducted

3.5.3.1. PAES may be initiated by the MAH/local responsible person or requested by the Authority. Conditions under which PAES are conducted by local responsible persons or MAHs are listed below:

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

3.5.3.2. All PAES should be approved by the Ethics Committees and the Authority.

3.5.3.3. The notification to the Authority shall be accompanied by cover letter, study protocol and ethics approval.

3.5.3.4. For investigator-initiated PAES, the notification to the Authority shall be accompanied by cover letter, study protocol, ethics approval and a written documentation to show support from the Local QPPV, local responsible person or MAH.

3.5.4. Study population

3.5.4.1. The PAES should ideally be conducted in a native Zambian population living in Zambia or in a study population to be determined in consultation with the Authority.

3.5.5. Study Design

3.5.5.1. The PAES design should be clearly defined in the study protocol. The choice of the study design will be based on the particular medicinal product and the scientific uncertainty to be addressed. The PAES should be feasible, ethically acceptable and of a design that can produce reliable and interpretable results in relation to the primary objectives. The design should take particular account of the post-authorisation setting and be feasible to complete within the indicated timeframe.

3.5.6. Roles and Responsibilities

3.5.6.1. Local responsible person or Marketing Authorisation Holder (MAH) shall:

i. Bear sole responsibility for all regulatory and technical aspects of the PAES.
ii. Appointing the Principal Investigator.
iii. Develop the study protocol following the format provided in section 3.4.8.
iv. Ensure that the PAES does not commence before all necessary authorisations are obtained.
v. Ensure the study is conducted in compliance with the approved protocol, good practices and applicable regulatory requirements.
vi. Ensure the final study report is submitted to the Authority not later than 12 months after the end of data collection.

3.5.6.2. Local QPPV

i. Submit notification for intention to conduct a PAES to the Authority by submitting a cover letter and protocol.
ii. Submit Individual Cases Safety Reports reported in the study to the Authority.
iii. Submit other safety reports and updates to the Authority.
iv. Submit a final study report to the Authority.

3.5.6.3. The Authority

i. A PAES in form of a clinical trial shall be approved in accordance with clinical trial guidelines.

ii. The Authority shall within, 60 calendar days, issue the applicant with a no objection letter if the submission meets the following conditions:

a. The PAES is not an interventional study or clinical trial.

b. Ethics approval has been obtained from an accredited ethics committee.

c. The arrangements in the study protocol including objectives, methods and reporting are appropriate, and

d. The study does not abrogate any other written law.

3.5.7. Study Protocol

3.5.7.1. All PAES must be conducted in accordance with approved protocol, good practices and all regulatory and ethical requirements.

3.5.7.2. Study protocols for PAES should consider relevant scientific guidance applicable to the issue to be investigated and the study design to be applied. The details of the study population or data source, details of the study design, milestones and all regulatory requirements should be included in the protocol.

3.5.7.3. Any amendment to the PAES protocol and study arrangements shall be submitted to the Ethics Committee(s) that originally approved the protocol and the Authority for approval before such amendments are carried out. Refer to clinical trial guidelines.

3.5.8. Reporting of adverse reactions/adverse events

3.5.8.1. Adverse reactions/adverse events should be reported to Authority. Procedures for the collection, management (including a review by local responsible person or the MAH if appropriate) and reporting of suspected adverse reactions/adverse events should be put in place and summarised in the study protocol.

3.5.9. Study reports

3.5.9.1. Progress Report

i. The progress report should be submitted in the format approved by the Authority. Refer to clinical trial guidelines.

ii. If a study is discontinued, the MAH/local responsible person should inform the Authority with reasons for the termination within 30 days of the termination of the study.

3.5.9.2. Final Report

i. The final study report should be submitted to the Authority no later than 12 months after the end of data collection.

ii. The final study report should follow the format specified in the clinical trial guidelines.

3.6. Signal Management

3.6.1. A Marketing Authorisation Holder is required to put in place mechanisms for signal detection and investigation of their medicines and allied substances, which should include:

3.6.1.1. A system for detecting and investigating safety issues (or signals) that may arise at any stage in the life cycle of a medicine or allied substance, including the clinical development, manufacturing or in the post-marketing setting in a timely manner;

3.6.1.2. Written procedures that adequately describes how a marketing authorisation holder shall perform signal detection, including:

i. Roles and responsibilities of each person involved in the signal detection process shall be clearly identified and documented;

ii. The source of the information to include in the analysis and the method used for signal detection shall be documented;

iii. Actions taken based on the outcome generated from the signal detection activities shall be documented adequately;

3.6.1.3. Data regarding changes of what is known about the risks and benefits of the medicine or allied substance shall be submitted to the Authority and documented; and

3.6.1.4. Safety monitoring activities shall include a review of cumulative cases, in order to allow for a comprehensive review of potential safety issues.

3.7. Safety Variations

3.7.1. Changes to safety aspects of approved labelling information, including Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Prescribing Information, must be notified to the Authority with a sample of the new labelling information for approval before implementation.

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

3.7.2.1. Covering letter addressed to the Director General

3.7.2.2. Tracked and clean versions of the document indicating the section where the change(s) have been affected.

3.7.2.3. Evidence supporting the need for the change.

Note: *Refer to the appropriate guidelines on amendments to marketing authorisation for further details.*

3.8. Safety Communication

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

3.8.2. Objectives of Safety Communication

3.8.2.1. Safety communication aims at:

i. Providing timely evidence-based information on the safe and effective use of medicines and allied substances;

ii. Facilitating changes to healthcare practices (including self-medication practices) where necessary;

iii. Improving attitudes, decisions and behaviour in relation to the use of medicines and allied substances;

iv. Supporting risk minimisation behaviour; and

v. Facilitating informed decisions on the rational use of medicines and allied substances.

3.8.2.2. Safety communication should support public confidence in the regulatory system.

3.8.3. Requirements for safety communications

3.8.3.1. All Safety Communication issued by the local responsible person, the MAH or any other person shall receive prior approval from the Authority. Application for approval shall include a copy of the proposed communication, the medium of distribution and the targeted audience(s).

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

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

3.8.4. Types of Safety Communication

3.8.4.1. Types of communication include, but are not limited to:

i. Dear Healthcare Professional (DHCP) letter

ii. Documents in lay language for patients

iii. Press communication or press releases

iv. Bulletins and newsletters

v. Responding to enquiries from the public

3.8.5. Content of Safety Communication

3.8.5.1. Safety communication should contain:

i. Identity of the person (MAH/local responsible person/other) issuing the safety notice

ii. Important emerging information on any authorised medicinal product which has an impact on the medicine's benefit-risk balance under any conditions of use;

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

iv. Any recommendations to healthcare professionals and patients on how to deal with safety concerns;

v. When applicable, a statement on the agreement between the MAH/local responsible person and the Authority on the safety information provided;

vi. Information on any proposed change to the product information (e.g. The summary of product characteristics (SmPC) or package leaflet (PL);

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

viii. Where relevant, a reminder of the need to report suspected adverse reactions in accordance with these guidelines.

4. References

1. Guidelines for Safety Monitoring of Medicinal Products, FDA Ghana
2. Guideline on good pharmacovigilance practices (GVP) Module VIII – PostAuthorisation safety studies (Rev 1), European Medicines Agency, 2013, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/ WC500129137.pdf
3. Guideline on good pharmacovigilance practices (GVP) Module XV – Safety communication, European Medicines Agency, 2013, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2 0 12/07/ WC500130396.pdf
4. Guidance for Industry and ZAMRA Staff, Dear Health Care Provider Letters: Improving Communication of Important Safety Information, US Food and Drugs Administration, 2014. http://www.ZAMRA.gov/downloads/drugs/guidancecomplianceregulatoryinformation/g uidanc es/ucm233769.pdf
5. Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2), 2012. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2C/ E2C_R2_Step4.pdf
6. Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 1), 2015. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/ WC500129134.pdf
7. Scientific guidance on post-authorisation efficacy studies. 12 October 2016. https://www.ema.europa.eu/documents/scientific-guideline/scientificguidancepost-authorisation-efficacy-studies-firstversion_en.pdf

Appendix I - Reporting Forms

Appendix Ia - Adverse reactions/event, medication errors and product quality problems

Z / MC / NPVU / F / 001 version 01 FORM No.: / A 0001

ADVERSE DRUG REACTION, MEDICATION ERROR AND PRODUCT QUALITY PROBLEM REPORTING FORM
(Identities of reporter and patient will remain strictly confidential)

NATIONAL PHARMACOVIGILANCE UNIT (NPVU)

Zambia Medicines Regulatory Authority
Plot No.2350/M, Off Kenneth Kaunda Int'l Airport Rd,
ZAF-KKIA Bypass Route between HITACHI & Delta Auto
P.O. Box 31890,
Lusaka, ZAMBIA

Telephone: +260 211 432 356 / 50
Mobile: +260 956 521 094
WhatsApp: +260 956 521 094
Email: npvu@zamra.co.zm
pharmacy@zamra.co.zm

1. PATIENT INFORMATION

Patient initials:..... File No.: ..... Age:..... Date of birth: ...../...../.....

Sex: Male ☐ Female ☐ Age of Pregnancy:.....Weight (kg):..... Height (cm): .....

2. DETAILS OF ADVERSE DRUG REACTION OR PRODUCT QUALITY PROBLEM OR MEDICATION ERROR

I am reporting on: 1. an Adverse Drug Reaction ☐ 2. a Product Quality Problem ☐ 3. a Medication Error ☐
4. Other (specify).....

Description of Adverse Drug Reaction or Product Quality Problem or Medication error:.....

.....

.....

Date Reaction Started: ...../...../.....

Outcome: Recovered ☐ Date:...../...../..... Recovering ☐ Not Yet recovered ☐ Unknown ☐

Seriousness of the adverse drug reaction: Death ☐ Life threatening ☐ Disability ☐ Birth defect ☐
Caused / prolonged hospitalization ☐ Other (specify).....

Additional information *(e.g. Relevant medical history, medicines taken in the last 28 days, allergies, previous exposure, baseline test results / lab data)*.....

.....

3. MEDICINES / VACCINES / MEDICAL DEVICES TAKEN / USED BY THE PATIENT: (✓) *Tick against the suspected Medicines / Vaccines / Medical Devices*

Indicate all medicines the Patient is taking

(✓)	Trade / Generic Name & Batch Number & Manufacturer	Dosage	Route of administration	Start date (dd/mm/yy)	Stop date (dd/mm/yy)	Reasons for use

4. DETAILS OF THE PRODUCT IF SUSPECTING PRODUCT QUALITY PROBLEM(S)

Trade / Brand Name	Batch Number	Dosage Form & Strength	Expiry Date (mm/yyyy)	Container size / type	No. of samples (if submitted)

Source / Supplier of the product:..... Manufacturer:.....

5. DETAILS OF THE REPORTER

Name: ..... Profession: ..... Signature: ..... Date (dd/mm/yyyy):.....

Institution/Facility:..... Phone: ..... Email:.....

Appendix Ib - Adverse events following immunisation

ZAMBIA REPORTING FORM FOR ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

AEFI Reporting ID: .....

**Patient name:*	**Reporter's Name:* .....
**Patient's full Address:*	Institution : .....
Telephone:	Designation &Department: .....
Sex: ☐M ☐F (if Female, ☐Pregnant ☐Lactating ☐N/A)	Address: .....
**Date of birth (DD/MM/YYYY):*	Telephone & e-mail:.....
OR Age at onset : ☐☐*Years* ☐☐ *Months* ☐☐☐ *Days*	Date patient notified event to health system (DD/MM/YYYY): .....
OR Age Group: ☐*< 1 Year* ☐ *1 to 5 Years* ☐ *>5 to 18 Years* ☐ *>18 to 60 Years* ☐ *>60 Years*	Today's date (DD/MM/YYYY): .....

Health facility (or vaccination centre) name:

Vaccine							*Diluent*		
**Name of vaccine (Generic)*	**Brand Name incl. Name of Manufacturer*	**Date of vaccination*	**Time of vaccination*	Dose (1st, 2nd, etc.)	**Batch/ Lot No.*	Expiry date	**Batch/ Lot No.*	Expiry date	Time of reconstitution

**Adverse event (s):*

☐ Severe local reaction ☐ *>3 days* ☐ *beyond nearest joint*
☐ Seizures ☐ *febrile* ☐ *afebrile*
☐ Abscess
☐ Sepsis
☐ Encephalopathy
☐ Toxic shock syndrome
☐ Thrombocytopenia
☐ Anaphylaxis
☐ Fever≥38°C
☐ Other (specify).....

Date & Time AEFI started (DD/MM/YYYY):
..... ☐☐ Hr ☐☐Min

Describe AEFI (Signs and symptoms):

**Serious: Yes / No ;* ➔ If Yes ☐ Death ☐ Life threatening ☐ Disability ☐ Hospitalization ☐ Congenital anomaly

**Outcome:* ☐ Recovering ☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Unknown

☐ Died If died, date of death (DD/MM/YYYY): ..... Autopsy done: ☐ Yes ☐No ☐Unknown

Past medical history (including history of similar reaction or other allergies), concomitant medication and dates of administration (exclude those used to treat reaction) and other relevant information (e.g. other cases). *Use additional sheet if needed :*

First Decision making level to complete:

Investigation needed: ☐ Yes ☐ No	If yes, date investigation planned (DD/MM/YYYY): .....

National level to complete:

Date report received at national level (DD/MM/YYYY):	AEFI worldwide unique ID: .....
Comments:	

**Compulsory field*
All completed forms should be emailed to the following email: **npvu@zamra.co.zm, aefizambia@gmail.com or**
WhatsApp: **+260 956 521094**
Address: *Zambia Medicines Regulatory Authority, Plot No. 2350/M, Off KK International Airport Road, P. O Box 31890 Lusaka, Zambia*

Appendix Ic – Blood transfusion reaction

Patient Transfusion Adverse Event Report Form

In the event of an adverse reaction following transfusion of blood or blood components, fill out this form and send to the **Hospital Blood Bank** and **ZAMRA** (Email: **npvu@zamra.co.zm**; or WhatsApp: **+260 956 521094**).

PATIENT INFORMATION		
Initials:	Date of Birth: dd/mm/yyyy	Age:
Sex: ☐ Male; ☐ Female	Blood Group:	
Hospital:	Ward:	
Patient File No.:	Blood Bank No.:	
Primary Diagnosis:		
Indication for Transfusion:		
Concurrent Medication:		

TRANSFUSION REACTION DETAILS		
Start of reaction: **Date:** dd/mm/yyyy **Time:** hh:mm	**End of reaction:** **Date:** dd/mm/yyyy **Time:** hh:mm	**Ongoing** ☐

Type of reaction: ☐ Non-serious ☐ Serious

Reason for Serious: ☐ Death ☐ Life-threatening ☐ Disabling or incapacitating ☐ Hospitalisation ☐ Congenital anomaly or birth defect ☐ Other (Specify): ……

Transfusion details:

Product Transfused	Pack Number	Expiry date	Blood Group	Date & Time Transfused	Product Warmed?	Transfusion Duration	Volume Transfused
				dd/mm/yyyy hh:mm			
				dd/mm/yyyy hh:mm			
				dd/mm/yyyy hh:mm			
				dd/mm/yyyy hh:mm			

Patient's vitals:

Pre-transfusion Vitals	Temp:	BP:	Pulse:	RR:	Sats:	Hb:
Post-transfusion Vitals	Temp:	BP:	Pulse:	RR:	Sats:	Hb:

Clinical Signs and Symptoms (tick as may apply)

☐ Chills/Rigors	☐ Dyspnoea	☐ Jaundice	☐ Back/flank pain
☐ Pyrexia: _____ °C	☐ Headache	☐ Dark urine	☐ Palpitations
☐ Nausea	☐ Chest pain/Tight chest	☐ Oliguria	☐ Blood Pressure reduced
☐ Vomiting	☐ Restlessness	☐ Purpura	☐ Blood Pressure increased
☐ Pruritus	☐ Attack of sweating	☐ Anxiety	☐ Unexplained bleeding
☐ Rash	☐ Bradycardia	☐ Vertigo	☐ Other: _____
☐ Urticaria	☐ Tachycardia	☐ Collapse/shock	☐ Other: _____

Suspected diagnosis

☐ Haemolytic reaction	☐ Viral transmission	☐ Post-transfusion purpura (PTP)
☐ Allergic reaction	☐ TRALI	☐ Graft-versus-Host disease
☐ Febrile reaction	☐ Transfusion-related dyspnoea	☐ Other: _____
☐ Bacterial reaction	☐ Hypervolaemia (TACO)	

Patient Outcome: (Could be filled in later)

☐ Recovered ☐ Recovered with complication	☐ Not yet recovered ☐ Unknown	☐ Died **Date:** dd/mm/yyyy **Time:** hh:mm

DETAILS OF THE REPORTER:

Reporter's Name:	Signature:	Date: dd/mm/yyyy
Profession:	Contact No.:	E-mail:
Facility Name:	Facility District:	

Appendix Id – Electronic reporting platforms

1. The '**Med Safety**' App available for download on Google Play Store and App Store
2. Online e-report on the Authority's website (www.zamra.co.zm)
   i. Reactions to medicines - https://vigiflow-eforms.who-umc.org/zm/adr
   ii. Reactions to vaccines - https://vigiflow-eforms.who-umc.org/zm/aefi

Appendix Id – Contact information for reporting

1. Email: npvu@zamra.co.zm
2. WhatsApp No. +260 956 521 094
3. Telephone No.: +260 211 432 356/50

Appendix II: Timelines

Appendix IIa: Reporting Timelines

Type of Safety Report	Time Frame for Reporting (Calendar days)	Format
Local Reports:		
a. Serious Adverse reaction or event that results in death	Within 7 days of becoming aware	ZAMRA Reporting form (Appendix I) or CIOMS 1 form or ICH E2B compliant
b. Serious Adverse reaction or event that does not result in death	Within 15 days of becoming aware	
c. Non-serious expected and unexpected adverse reactions	Within 30 days of becoming aware	
d. Literature reports that affect the safety of the product	Within 15 days of becoming aware	Detailed report plus copy of the publication(s)
Foreign Reports:		
e. Foreign regulatory decisions that affect	Within 15 days of becoming aware	Detailed report
f. Literature reports that affect the safety of the product	Within 15 days of becoming aware	Detailed report plus copy of the publication(s)
g. Notification of change in nature, severity or frequency of risk factors	Within 30 days of becoming aware	Detailed report
h. New information from clinical trials or other studies impacting the benefit-risk profile of the product	Within 30 days of becoming aware	Detailed report
i. PSURs/PBRERs	• For New/Chemical Entities (NCEs) - Six (6) monthly for the first two years after grant of MA; - Annually for 3 years thereafter; - At renewal of MA; - upon request by the Authority. • For all other products at renewal of MA	PSUR – ICH E2C PBRER – ICH E2C (R2)

Appendix IIa: Feedback Timelines

Type of Safety Report or notification	**Type of Feedback**	**Time Frame (Calendar days)**	**Format/means**
a. Adverse reaction/event reports	Acknowledge receipt	Within 15 days of receipt	Phone or e-mail.
	Causality assessment	Within 30 days of evaluation	Letter
b. Quality Problem Reports	Acknowledge receipt	Within 15 days of receipt	Phone or e-mail.
	Causality assessment	Within 30 days of analysis or evaluation	Letter
c. Risk Management Plans, PSURs (or PBRERs)	Acknowledge receipt and communicate preliminary evaluation comments	Within 30 days of analysis or evaluation	Letter
d. Post-Authorisation Study	Decision	Within 60 days of receipt	Letter

Appendix III: Risk Classification of Product Quality Problems

CLASS	DESCRIPTION	EXAMPLES
I	For dangerous, defective, and potentially life-threatening medicines that could result into serious health risks, adverse events, or even death.	• Wrong Product (label and contents are different products) o Correct product but wrong strength, with serious medical consequences o Microbial contamination of sterile injection or ophthalmic product o Chemical contamination with serious medical consequences o Mix-up of some products with more than one container involved o Wrong active ingredient in a multi-component product with serious medical consequences o Lack of effectiveness for a life-threatening condition
II	For products that could cause temporary or medically reversible adverse health problems or mistreatment.	• Mislabeling e.g. wrong or missing text or figures o Missing or incorrect information o Leaflets or inserts o Microbial contamination of non-injectable, non-ophthalmic sterile product with medical consequences o Chemical/ physical contamination (significant impurities, cross-contamination, particulates) o Mix-up of products in containers o Non-compliance with specification (e.g. assay, stability, fill/ weight or dissolution) o Insecure closure with serious medical consequences (e.g. cytotoxics, child-resistant containers, potent products) o Lack of efficacy/ effectiveness for a medical condition that is not life-threatening
III	For products that are defective but are unlikely to cause or pose a significant health risk or which do not comply with the requirements of the Act in relation to quality, safety or efficacy.	• Faulty packaging e.g. wrong or missing batch number • Faulty closure • Contamination- microbial spoilage, dirt or detritus, particulate matter

5. Amendment Sheet

Date identified	Amendment identified by	Short description of the changes proposed to the document	Review of proposed amendment