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PHARMACY AND POISONS BOARD

GUIDELINES ON THE SAFETY AND VIGILANCE OF HEALTH PRODUCTS AND TECHNOLOGIES

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Abbreviations and Acronyms

ACT	Artemisinin Based Combination Therapy
ADR	Adverse Drug Reaction
AE	Adverse event
AEFI	Adverse event following immunization
AMR	Antimicrobial resistance
BCG	Bacille Calmette-Guérin Vaccine
CHMT	County Health Medical Team
DLP	Data Lock Point
DTP	Diphtheria, Tetanus toxoids and Pertussis vaccine
EAC	East African Community
ECCT	Expert Committee on Clinical Trials
EPI	Expanded Program on Immunization
FBO	Faith based organization
IBD	International Birth Date
ICH	International Conference on Harmonization
IEC	Information, Education and Communication
KMA	Kenya Medical Association
KNBTS	Kenya National Blood Transfusion Service
KPA	Kenya Pharmaceutical Association
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Measles, Mumps, Rubella vaccine
MOH	Ministry of Health
MSH	Management Sciences for Health
NASCOP	National Aids and STI Control Program
NNAK	National Nurses Association of Kenya
NGO	Non-governmental organization
NLTP	National Tuberculosis, Leprosy and Lung Disease Program
NTDP	Neglected Tropical Diseases Program
NMCP	National Malaria Control Program
NRA	National Regulatory Authority
NVIP	National Vaccines and Immunization Program
NVSAC	National Vaccine Safety Advisory Committee
OPV	Oral Polio Vaccine
OTC	Over the counter
PBRER	Periodic Benefit/Risk Evaluation Report
PERAC	Pharmacovigilance Expert Review Advisory Committee
PHP	Public Health Program
PPB	Pharmacy and Poisons Board
PSUR	Periodic Safety Update Report

PSK	Pharmaceutical Society of Kenya
PV	Pharmacovigilance
PvERS	Pharmacovigilance electronic reporting system
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk management plan
SCHMT	Sub-County Health Medical Team
SAE	Serious Adverse Event
SCIT	Sub- County Investigation Team
SUSAR	Suspected Unexpected Serious Adverse Reaction
UMC	Uppsala Monitoring Centre
WHO	World Health Organization

Glossary of terms
The following definitions describe terminologies in the context of this guideline.

Active surveillance - Active measures are taken to detect adverse events. It involves active follow-up after treatment where the events may be detected by asking patients directly or screening patient records. It is best done prospectively. Active pharmacovigilance is sometimes very descriptively referred to as, "hot pursuit"

Adverse Event/ Adverse Experience - Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse event following immunization (AEFI) - Any untoward medical occurrence which follows immunization and which, does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

Adverse Drug Reaction - A response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function. An adverse drug reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medical product and an occurrence is suspected.

Board - The Pharmacy and Poisons Board

Case Control Study - Study that identifies a group of persons with the unintended drug effect of interest and a suitable comparison group of people without the unintended effect. The relationship of a drug to the drug event is examined by comparing the groups exhibiting and not exhibiting the drug event with regard to how frequently the drug is present.

Cohort Event Monitoring (CEM) - A prospective, observational, cohort study of adverse events associated with one or more medicines

Clinical Trial - A systematic study on pharmaceutical health products in human subjects (including patients and other volunteers) in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the objective of ascertaining their efficacy and safety. Clinical trials are generally classified into Phases: I to IV. Phase IV trials are studies performed during marketing of the pharmaceutical/medical product. They are carried out on the basis of the product characteristics for which the marketing authorization

was granted and are normally in the form of post-marketing surveillance.

Cohort Study - A study that identifies defined populations and follows them forward in time, examining their rates of disease. A cohort study generally identifies and compares exposed patients to unexposed patients or to patients who receive a different exposure.

Complementary/ Alternative Medicine - These terms are used interchangeably with traditional medicine in some countries. They refer to a broad set of healthcare practices that are not part of that country's own tradition and are not integrated into the dominant health care system. They have not usually been tested in specified clinical indications by an objective scientific discipline.

Data Lock Point – Date designated as the cut-off for data to be included in the periodic safety update reports (PSUR), based on the international birth date (IBD).

Drug - In this context also known as medicine or medical product

Drug Alerts - The action of notifying a wider audience than the initial information holder(s) of a suspected association between a drug and an adverse reaction. Note that the term is used in different contexts that can be confusing, for example, an alert may be from a manufacturer to a regulator or from a regulator to the public.

E-shot – Email communication sent from PPB to the healthcare providers, pharmaceutical industry, marketing authorization holders, public health programs on any adverse events, reactions and poor-quality medicines.

Field Safety Corrective Action (FSCA) - An action taken by a manufacturer to reduce a risk of death or serious deterioration in the state of health associated with the use of a medical device that is already placed on the market. Such actions should be notified via a field safety notice.

Field Safety Notice (FSN) - A communication to customers and/or users sent out by a manufacturer or its representative in relation to a Field Safety Corrective Action.

Healthcare providers/professionals – In the context of this guideline, include medical doctors, dentists, pharmacists, clinical officers, pharmaceutical technologists, nurses, community health workers and medical laboratories staff.

Health product - Any substance or combination of substances, which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings.

Health technology - Also known as medical device including in vitro diagnostics.

Herbal medicines - Include herbs, herbal materials, herbal preparations and finished herbal products, that contain as active ingredients parts of plants, or other plant materials, or combinations.

Identified risk – An undesirable clinical outcome and for which there is sufficient scientific evidence that it is caused by the medical product.

Important identified risk and important potential risk - An identified risk or potential risk that could have an impact on the risk-benefit balance of the medical product.

Individual case safety report (ICSR) – Also known as a suspected adverse drug reaction report containing information on the patient, drug reaction, suspected drug/medicine/vaccine/medical device and the reporter.

International birth date (IBD) – The date of the first marketing approval for a medical product in any country in the world. This is in relation to the submission of Periodic safety update reports (PSURs) to the National Regulatory Authority (NRA).

In vitro diagnostics (IVD)-Means a medical device, whether used alone or in combination, intended by the manufacturer for the in-vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes

Lack of Efficacy - Unexpected failure of a drug to produce the intended effect as determined by previous scientific investigation.

Marketing Authorization Holder (MAH) – An individual or a corporate entity/ company responsible for placing a pharmaceutical product in the market either through importation, donation, distribution or sale in Kenya. This individual or company is responsible for all aspects of the product, including quality and compliance with the conditions of the marketing authorization.

Manufacturer - A person or a body who sells a product under their own name, or under a trademark, design, trade name or other name or mark owned or controlled by the person or the body, and who is responsible for designing, manufacturing, assembling, processing, labelling, packaging, refurbishing or modifying the product, or for assigning to it a purpose, whether those tasks are performed by that person or on their behalf.

Medical device - Any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use or calibrator, software, material or other similar

or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purposes(s) of:

a. Diagnosis, prevention, monitoring, treatment or alleviation of disease;
b. Diagnosis, monitoring, treatment, alleviation of or compensation for an injury;
c. Investigation, replacement, modification or support of the anatomy or of a physiological process;
d. Supporting or sustaining life;
e. control of conception;
f. Disinfection of medical devices;
g. Providing information by means of in vitro examination of specimens derived from the human body,

and, which does not achieve its primary intended action by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

Medication error - An unintended failure in the drug treatment process that leads to, or has the potential to lead to harm to the patient.

Mutual Recognition Agreement - A principle of international law whereby states party to mutual recognition agreements recognize and uphold legal decisions taken by competent authorities in another member state. Mutual recognition is a process which allows conformity assessments (such as, of qualifications and products) carried out in one country to be recognized in another country.

National Pharmacovigilance Centre - A single, government recognized centre (or integrated system) within a country with the clinical and scientific expertise to collect, collate, analyse and give advice on all information related to drug safety.

Periodic Safety Update Report (PSUR) - An update of the world-wide safety experience of a product obtained at defined times post marketing authorization.

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

Pharmaceutical industry- Refers to the manufacturers, marketing authorization holders, local technical representatives, distributors, parallel importers.

Pharmacoepidemiology - The study of the use and effects of drugs in large numbers of people.

Pharmacovigilance - The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. Also known as Vigilance to include blood and blood products and health technologies.

Potential risk - An undesirable clinical outcome and for which there is scientific evidence to suspect the possibility of a causal relationship with the medical product

Prescription Event Monitoring - A system created to monitor adverse drug events in a population. Prescribers are requested to report all events, regardless of whether they are suspected adverse events, for identified patients receiving a specified drug.

Qualified Person for Pharmacovigilance (QPPV*)* - An individual named by a Marketing Authorization Holder (MAH) as the main person responsible for ensuring that the company (the MAH) meets legal obligations for monitoring of the safety and quality of the product marketed in Kenya.

Recognition - Acceptance of the regulatory decision of another regulator or trusted institution. Recognition should be based on evidence that the regulatory requirements of the reference regulatory authority are sufficient to meet the regulatory requirements of the relying authority. Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement.

Reliance - The act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision. The relying authority remains independent, responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others.

Risk-Benefit Balance - An evaluation of the positive therapeutic effects of the medical product in relation to the risks (any risk relating to the quality, safety or efficacy of the medical product as regards patients' health or public health.

Risk Management Plan (RMP) - A detailed description of the risk management system; includes information on a medicine's safety profile; how its risks shall be prevented or minimized in patients; plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine and measuring the effectiveness of risk-minimization measures.

Risk management system - A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks

relating to a medical product, including the assessment of the effectiveness of those activities and interventions.

Risk minimisation measure (synonym: Risk minimization activity) - Interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur.

Safety concern – An identified risk, important potential risk or missing information (refer to their respective definitions above).

Signal - Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the event and the quality of the information.

Serious Adverse Event – These are adverse events that resulted one or more of the following outcomes; Death, Disability, Hospitalization/Prolonged Hospitalization, Congenital Anomaly or those that are life threatening. For medication errors, these are events that reached the patients and caused harm or death.

Unexpected Adverse Reaction - An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug.

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These guidelines have also been domesticated from the 'EAC Harmonized Compendium on Safety and Vigilance of Medical Products and Health Technologies, 2019.'

Foreword

The World Health Organization defines Pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The scope of Pharmacovigilance continues to widen to include reporting of adverse events due to blood products, biologicals, vaccines, health technologies, herbal products, traditional and complementary medicines and cosmeceuticals hence the term "Vigilance".

The mandate of the Pharmacy and Poisons Board is to ensure the provision of quality, safe and efficacious Health Products and technologies. Quality Health Products and Technologies are a central component in the attainment of Universal Health Coverage (UHC) in Kenya. Despite their obvious benefits, they are known to have a possibility of causing adverse events which can be serious or even fatal. The safety and quality of these Health Products and Technologies must be continuously monitored by key players in the industry to ensure patients' safety.

This document is, therefore, intended to provide guidance to all healthcare professionals, patients, marketing authorization holders, and the public on the reporting of adverse drug reactions and adverse events in health products and technologies in Kenya.

The Pharmacy and Poisons Board shall continue to raise awareness, conduct training, and sensitize the public and healthcare professionals on the importance of reporting ADRs and AEs. This guideline and reporting tools shall continue to be updated periodically, taking into consideration continuous monitoring and evaluation and emerging research findings and lessons learned.

1. INTRODUCTION

1.1. Background

The World Health Organization (WHO) defines Pharmacovigilance (PV) as the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems."

Pharmacovigilance aims at achieving the following:

a. Improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions;
b. Improve public health and safety in relation to the use of Health Products and Technologies (HPTs);
c. Detect problems related to the use of HPTs and communicate the findings in a timely manner;
d. Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, leading to the prevention of harm and maximization of benefits;
e. Encourage the safe, rational and more effective (including cost effective) use of HPTs;
f. Promote understanding, education and clinical training in Pharmacovigilance and its effective communication to the public.

Monitoring the safety of health products and technologies including vaccines -, their quality and effectiveness following market authorization, in addition to providing medicines safety information are essential functions of national healthcare systems. These are responsibilities of the national regulatory authorities (NRAs), healthcare providers across all levels of the healthcare system as well as other stakeholders, among them, public health programs (PHPs), and the pharmaceutical industry, including marketing authorization holders (MAHs).

The Pharmacy and Poisons Board (PPB) as the National Pharmacovigilance Centre has the responsibility to collect, collate, assess causality of safety reports, conduct risk management and communication in addition to

contributing these reports to the international database for ADRs at the Uppsala Monitoring Centre-WHO Collaborating Centre for International Drug Monitoring, Sweden. The Board has since 2009, when the PV centre was established, intensified its safety monitoring activities including training and sensitization of healthcare professionals and other stakeholders on reporting of both ADRs and poor-quality medicines.

a) The importance of Pharmacovigilance

The information collected during the pre-marketing phase of drug development is inevitably incomplete with regard to possible adverse drug reactions (ADRs). This is mainly because:

a. Tests in animals are insufficient to predict human safety;
b. Patients used in clinical trials are selected and limited in number, the conditions of use differ from those in clinical practice and the duration of trials is limited;
c. By the time of licensing exposure of less than 5000 human subjects to a drug allows only the more common ADR to be detected;
d. At least 30,000 people need to be treated with a drug to be sure that you do not miss at least one patient with an ADR, which has an incidence of 1 in 10,000 exposed individuals;
e. Information about rare but serious adverse reactions, chronic toxicity, use in special groups (such as children, the elderly or pregnant women) or drug interactions is often incomplete or not available; Thus, post-marketing surveillance is important to permit detection of less common, but sometimes very serious ADRs.

Health care providers shall therefore report on all suspected adverse events as this can save lives of their patients and others.

1.2. The Legal Framework

The Health Laws (Amendment) Act, 2019 and the Pharmacy and Poisons Act, Cap 244, Laws of Kenya mandates the Pharmacy and Poisons Board (PPB), to regulate Health Products and Technologies in Kenya. The Board ensures

quality, safety and efficacy of Health Products and -Technologies in the Kenyan market.

The Kenya National Pharmaceutical Policy, 2008 acknowledges the role of the Pharmacy and Poisons Board (PPB) in regulation of pharmacovigilance, establishing effective Pharmacovigilance systems and enhancing the participation of the pharmaceutical industry, the private sector, health professionals and consumers in post-market surveillance and pharmacovigilance in Kenya.

Legal notice no. 96 on the Pharmacy and Poisons (Pharmacovigilance and Post market surveillance) Rules, 2022.

1.3. Scope

These guidelines provide practical technical guidance for the continuous safety monitoring of Health Products and Technologies in Kenya. It applies to all entities with marketing authorisation for their products in Kenya. They include but are not limited to the manufacturers, marketing authorization holders (MAH), local technical representatives, importers and donors of HPTs. It also applies to the other key stakeholders like the public, health care professionals, County governments, public and private institutions involved in patient care.

The guidelines provide information on the reporting requirements for the different stakeholders, training and capacity building and communication of safety related issues.

2. THE NATIONAL PHARMACOVIGILANCE SYSTEM

The National Pharmacovigilance System was officially launched in June 2009 and falls under the Pharmacy and Poisons Board. It includes;

a. The National Pharmacovigilance Centre based at the Pharmacy and Poisons Board, along Lenana road, opposite the Department of Defence

(DoD).

b. The National Spontaneous Reporting system which has both the electronic and manual pharmacovigilance reporting forms.
c. The national database and;
d. The Pharmacovigilance Experts Review and Advisory Committee (PERAC) and the National Vaccines Safety Advisory Committee (NVSAC) provide technical assistance on causality assessment, risk assessment, risk management, case investigation, and risk communication. In addition, they shall make appropriate recommendations to the Chief Executive Officer, PPB, and the Ministry of Health.
e. The Risk Communication Plan

The PV system also includes public, private, and NGO/Mission healthcare providers, public health programs, the pharmaceutical industry, and marketing authorization holders.

The National Pharmacovigilance Centre shall:

a. Develop and maintain the databases for ICSRs;
b. Through the National PV system collect, manage, assess, analyse, identify signals and communicate safety information related to HPTs authorised by the Board;
c. Support County and Subcounty to investigate relevant ADR /AEs reports;
d. Share ADRs and AEs on HPTs to Uppsala Monitoring Centre (UMC);
e. Provide feedback to the stakeholders on reported adverse events
f. Conduct advocacy, training and education on Pharmacovigilance related issues;
g. Develop and disseminate Information, Education and Communication (IEC) materials;
h. Implement appropriate regulatory framework to support PV activities;
i. Conducting assessment, audit and Pharmacovigilance inspections of the pharmaceutical industry
j. Conduct risk communication to the stakeholders including the general public.

3. ROLES AND RESPONSIBILITIES OF KEY PLAYERS

The entire system of pharmacovigilance works with the support of each healthcare provider, the regulatory bodies, the pharmaceutical industry, MAHs, PHPs, other stakeholders and the public at large.

3.1. Stakeholders

3.1.1. Patient/Public

Patients and members of the public are encouraged to follow prescribed treatment and report any suspected adverse effects of medicines, vaccines and medical devices or suspected poor-quality product dispensed to them. They can report to a healthcare provider or the nearest health facility or directly to the Board by telephone +254795743049 or email at pv@ppb.go.ke or dialling the **USSD code *271#** or the public reporting form at https://pv.pharmacyboardkenya.org/padrs/add

3.1.2. Health care provider

Patient awareness of possible serious reactions, and development of a culture to report reactions are essential for any pharmacovigilance system. Health facility staff provide an essential link in the detection of adverse drug reactions (ADRs) and adverse events (AEs) at the periphery of the healthcare system. The healthcare provider shall:

a. Conduct patient education on ADRs and AEs including medication use counselling.
b. Diagnose/detect and initiate appropriate clinical management and treatment of patients presenting with adverse reactions and/or events
c. Report **ALL** ADRs and AEs :
    i. Send the filled reporting forms immediately to the County Vigilance focal person or;
    ii. Directly through the Pharmacovigilance Electronic Reporting System (PvERS) at www.pv.pharmacyboardkenya.org or;
    iii. Through the mPvERS mobile application found on Play Store for Android and App Store for iPhone operating system (iOS).
d. Utilise the collated data on ADRs and AEs for decision making at the

facility level.

e. Promote rational drug use.
f. Participate in capacity building of other healthcare providers and public on safety monitoring of HPTs.

3.1.3. County/Sub - County Investigation Teams

The County/Sub – County Investigation Teams (SCIT) shall comprise of members from the County Health Management Team (CHMT) and Sub-County Health Management Team (SCHMT) including the County vigilance focal person. They shall investigate and follow up on serious ADRs and AEs within the respective Counties. The SCIT may comprise of the Sub-County pharmacist, Sub-County public health nurse, Sub-County public health officer, Sub-County laboratory in-charge, Sub-County hemovigilance officer and any other relevant specialist where applicable. An additional two representatives from the Board and the respective Public Health Program (PHP) may form part of the team during these investigations.

The findings of the investigations shall be forwarded to the Pharmacovigilance Expert Review and Advisory Committee (PERAC) or the National Vaccines Safety Advisory Committee (NVSAC) as applicable. They shall give their expert opinion and thereafter issue recommendations, which may include regulatory actions and other risk minimization activities to prevent further harm.

3.1.4. County Governments

The County governments shall, in collaboration with the Ministry responsible for matters related to health and the Board:

a. Plan and budget for pharmacovigilance activities at county level;
b. Implement pharmacovigilance and post market surveillance activities within the county;
c. Coordinate and participate in the investigations of serious adverse reactions, events, signals and quality defects of health products and technologies;
d. Conduct post market quality surveys of health products and technologies;

e. Submit safety reports and reports on suspected poor quality health products and technologies to the Board within the prescribed timelines;
f. Notify the Board in cases of quality defects that have high public health impact including quality defects that affect vaccines and other biological products within twenty-four hours;
g. Notify the Board on serious adverse events and serious adverse reactions within twenty-four hours;
h. Participate in training of healthcare professionals and the public on pharmacovigilance and post market surveillance in the county in collaboration with the other stakeholders;
i. Facilitate dissemination of feedback on pharmacovigilance and post marketing surveillance including information on product quarantine or recalls within 24 hours of receipt of communication, from the Board to the health care professionals where necessary; and
j. collaborate with the National Pharmacovigilance and Post Marketing Surveillance Technical Working Group established under these Rules.

The County Governments shall designate a County Vigilance focal person to coordinate the implementation of the pharmacovigilance and post market surveillance activities within the County in collaboration with the Board.

3.1.5. County Vigilance Focal Person

The County Vigilance Focal Person shall:

a. Receive filled reporting forms from health facilities within the County and immediately enter them onto the PvERS at www.pv.pharmacyboardkenya.org
b. Participate in the investigations of serious ADRs and AEs together with the investigation teams at the County or Sub-County level.
c. Provide a summary of vigilance reports on Health Products and Technologies to the CHMT.
d. Participate in training County healthcare staff in collaboration with the Board and PHPs.
e. Participate in Pharmacovigilance and Post market surveillance related

activities in the County.

3.1.6. Public Health Programs

The Ministry of Health through its designated Public Health Programs (PHPs) and in collaboration with the Board shall:

a. Provide public information during the launch of new drug regimens;
b. Ensure training of health facility staff in use of medicines or regimens and monitoring for any adverse events that may arise;
c. Conduct passive and active surveillance of Health Products and Technologies (HPTs) in collaboration with the Board;
d. When necessary, be called upon by the Board and to determine the benefit risk assessment of HPTs, in order to update treatment guidelines and initiate new training and communications to health providers and the general public;
e. Provide technical support to the investigation teams on quality and safety issues at the County and Sub-County levels;
f. Conduct post-marketing quality surveys of Health Products and Technologies;
g. Participate in activities of the National Pharmacovigilance and Post-marketing surveillance Technical Working Group;
h. Make programmatic decisions as concerns matters related to quality, safety and efficacy of Health Products and Technologies;
i. Conduct education, training and advocacy to the relevant stakeholders;
j. Plan and budget for pharmacovigilance activities; and
k. Mobilize resources for pharmacovigilance and post marketing surveillance activities.

3.1.7. Pharmacovigilance Sentinel Sites

It is recognized that the National Pharmacovigilance System will collect, as a passive method, a wide variety of data on ADRs and AEs. However, some specific 'programmatic' interests may not be met. Therefore, specific sentinel sites have been established for active surveillance as required under authority of the Board, and in collaboration with the PHPs to carry out the following functions:

a. Detailed investigations to gather specific data;
b. Verification of specific reports/ claims;
c. Cohort event monitoring;
d. Conduct case control studies;
e. Establish and maintain pregnancy registries, disease or drug registries;
f. Specific pharmacoepidemiology studies/analysis; and
g. Utilize any other methods required to collect relevant information.

The protocols for such sentinel sites shall be developed in conjunction with the Board, and where necessary gain the necessary scientific ethical clearance and consent of approved Ethics Committees, Institutional Review Boards and the Expert Committee on Clinical Trials (ECCT) at the Board where relevant.

The data shall be made freely available, on a regular basis, to the Division of Pharmacovigilance at the Board. The Pharmacy and Poisons Board remains responsible for all aspects of pharmacovigilance but may work with an appropriate partner to set up additional relevant sentinel sites where necessary.

3.1.8. Pharmaceutical industry/MAHs

The MAHs shall submit post-marketing surveillance data, PBRERs, PSURs and any local reports on ADRs and AEs, which are brought to their attention, whether reported spontaneously by healthcare professionals or consumers or occurring in the context of a post-authorization study, with the Board within the timelines stipulated in this guideline. They may also be called upon to meet the costs of specific investigations and/or regulatory actions affecting their products. Specifically, they shall implement directives of the Board and fund Pharmacovigilance activities and other investigations on their products.

The MAH shall have at its disposal, an appropriately qualified person responsible for pharmacovigilance, resident in Kenya.

3.1.9. Qualified Person for Pharmacovigilance

A qualified person for pharmacovigilance (QPPV) acts on behalf of the MAH as

a single point of contact for the Board on all matters relating to pharmacovigilance and safety of their marketed products. The roles and responsibilities of the QPPV shall be as per the *Guidelines for the Establishment of Qualified Persons for Pharmacovigilance (HPT/PDS/VMS/GUD/006 Revision 1*).

3.1.10. Pharmacovigilance Experts Review and Advisory Committee (PERAC)

The PERAC consists of core members drawn from the following specialities: Pharmacoepidemiology and Pharmacovigilance; Clinical Pharmacy; Paediatrics; Epidemiology; Drug discovery and development; Immunology; Pathology; Internal medicine; Vaccinology; Haematology; Obstetrics and gynaecology; Pharmacology and Toxicology. Where specialized expertise is required and not available in the committee, then such expertise may be sourced on an ad hoc basis to support the PERAC in advice or recommendations in accordance with the procedure established by the PERAC. The PPB PV division is the secretariat of the committee. The members shall be appointed by the Chief Executive Officer, PPB. They shall serve for a period of three years that shall be subject to renewal. The terms of office shall be in accordance with set terms of reference of the PERAC committee.

3.1.11. Role of the PERAC

The PERAC shall be responsible for assessing all aspects of risk management of HPTs, including:

a. The detection, assessment, minimization and communication of the risk of adverse drug reactions and adverse events while taking the therapeutic effect of the same into account;
b. Evaluation of protocols and reports on PASS and PAES;
c. Provide guidance on pharmacovigilance audits and act as a peer review for the reports
d. Assist the investigation teams where required; and

e. Providing recommendations on pharmacovigilance and risk management systems, including the monitoring of their effectiveness, to the Director, HPT and the CEO.

Once recommendations are received from the PERAC, the Board shall take responsibility for any regulatory action with respect to the implicated health product or technology. These actions shall be officially communicated to all stakeholders who have liability for the product.

3.1.12. National Vaccine Safety and Advisory Committee (NVSAC)

The constitution, roles and responsibilities of NVSAC shall be as per the Guideline for Monitoring, Reporting and Management of AEFIs in Kenya.

3.1.13. The National Pharmacovigilance and Post-marketing surveillance technical working group

The National PV/PMS TWG shall:

a. Provide technical guidance for the implementation of pharmacovigilance and post-marketing quality surveillance activities to ensure quality, safe and efficacious HPTs;
b. Mobilize partners and advocate for funds for pharmacovigilance and post marketing surveillance research and surveys;
c. Identify the logistical and resources needs for the implementation of pharmacovigilance and post-marketing quality surveillance activities;
d. Provide a forum for private and public sector groups to consider and recommend policy direction on pharmacovigilance and post marketing surveillance program in Kenya;
e. Provide a platform for the review and dissemination of reports on status of pharmacovigilance and post-marketing quality surveillance in Kenya.

3.2. Collaboration & Reliance in Vigilance-Related Decisions

The Board shall continue to ensure the safety of marketed products through its established vigilance system. To ensure that safety issues are promptly

identified and the necessary interventions implemented, the Board shall consider decisions from well-resourced regulatory authority (ies)/WHO-listed authorities (WLA) on the safety of HPTs that negatively impact the health of patients. The regulatory decisions of the Board leveraging on safety decisions from well-resourced or reference regulatory authority (ies) shall be geared towards ensuring appropriate and safe use of registered (or EUA-granted) health products. Where applicable, assessment reports shall be shared with the Board by the Reference Regulatory Authority or WHO.

3.2.1. Reliance

To enhance efficiency in Pharmacovigilance regulatory oversight, the Board shall implement reliance as follows:

a) Aggregate reports

The Board shall leverage the expertise, assessments and decisions of stringent regulatory authorities and WHO regarding the aggregate PV reports for regulatory decision-making.

b) Good Pharmacovigilance Practice inspections

The Board shall use mutual recognition and reliance mechanisms for GVP inspection outcomes while ensuring compliance with local regulatory requirements. This includes outcomes from WLA inspections and regional initiatives such as the African Medicines regulatory harmonization (AMRH). This approach aims to minimize duplication of efforts and optimize the use of resources.

For products of any other emergency or public health concern, where mutual recognition agreements exist, the reliance approach shall also be used for PV inspections. For WHO-prequalified emergency use-listed vaccines and other HPTs, WHO inspection outcomes will also be used for PV inspections.

c) Post Authorization studies (PASS & PAES)

The Board may require market authorization holders to undertake Post-authorization Safety Studies (PASS) to address issues that are specific to Kenya, either identified in the RMP or at the time of RMP assessment, for example, to compare safety profiles and highlight differences in specific

populations, such as ethnic groups. Where possible, the Board shall require that the PASS/PAES protocol used by product manufacturers be agreed upon with the reference to National or Regional regulatory authorities to facilitate the implementation of multi-country PASS.

d) Safety alert communications

The Board shall assess safety alert communications from WHO-Listed Authorities (WLA) and WHO, as appropriate, and communicate them to the relevant stakeholders to minimize risks and prevent harm to the public.

Exemptions from reliance

The following areas shall be exempted from reliance: Management of Kenya's data on adverse events and disease epidemiology in specific populations, Kenya's spontaneous reporting systems, assessment of AEFIs and adverse events reported nationally and reporting to VigiBase, some risk communication to the public and health care workers, information on the distribution system and statistics on HPTs exposure and some risk minimization measures specific to the country's context.

3.2.2. Collaboration

The Board shall work closely with other regulatory authorities at regional and international levels, development partners, and the World Health Organization to enhance the safety surveillance of HPTs. This collaboration will include capacity building and sharing information on safety issues and anticipated regulatory actions.

Kenya shall participate in the WHO Programme for International Drug Monitoring (PIDM) and will contribute to the WHO global database of individual case safety reports (VigiBase) developed and maintained by the Uppsala Monitoring Centre (UMC), which is the WHO Collaborating Centre for International Drug Monitoring. The Board shall share the safety data and rely on this resource (and thereby, on each other's data) as a single point of pharmacovigilance information, to confirm or validate signals of adverse events with health products in the country.

The Board shall also rely on the regional pharmacovigilance databases, including those already available as a subset of VigiBase. These databases may also assist the Board in utilizing safety data on products of mutual interest and products specific to the region.

3.3. Stakeholder Engagements

Stakeholder engagement is crucial in pharmacovigilance to ensure comprehensive drug safety monitoring and improve patient outcomes by fostering knowledge exchange and collaboration among all involved parties. Below are some of the stakeholder engagement approaches utilized at the National Pharmacovigilance Centre.

i) Regular Stakeholder Engagement Meetings

The Board shall organize periodic stakeholder meetings, workshops, and roundtable discussions with representatives from pharmaceutical companies, healthcare professionals, patient organizations, academia, and public health programs. These engagements shall enable stakeholders to provide insights into the performance of the PV system, regulatory challenges, safety concerns related to Health Products and Technologies, and queries about the Pharmacy and Poisons Rules, 2022.

Some of the regular stakeholder engagements include;

a) Annual County Vigilance Focal Person Meetings
b) Quarterly Meetings with the Public Health Programs
c) Biannual Meetings with the MAH(s), e.g., KAPI, FKPM,
d) Annual PV/PMS Technical Working Group Meeting
e) Annual World Patient Safety Day
f) Annual Med Safety Week in collaboration with WHO Upsala Monitoring Centre
g) Pharmacovigilance Training
h) Quarterly NVSAC/PERAC Meetings

Ad hoc stakeholder engagement meetings shall be held on a need basis. All stakeholders can express interest in holding a stakeholder engagement with

the National Pharmacovigilance Centre by writing to pv@ppb.go.ke.

ii) Stakeholder Participation and Call for Input

The Board shall conduct stakeholder participation when developing or revising PV regulations, guidelines, or pharmacovigilance materials. Relevant stakeholders shall be invited to submit written feedback, which shall be analyzed and incorporated into regulatory decisions.

Stakeholders can also provide unsolicited feedback on PV regulations and guidelines by writing to pv@ppb.go.ke.

iii) Feedback from Reporting Systems

The Board shall acknowledge receipt of safety reports. The PvERS has an interactive feedback function that allows reporters to provide feedback regarding ICSRs.

The Board shall publish safety communication, such as quarterly pharmacovigilance summaries, safety alerts, and additional risk minimization measures, on the PPB Website. Communication shared on the website shall be sent to all stakeholders on the National Pharmacovigilance Centre mail list as an E-shot. For any inquiries or feedback on the published communication, the stakeholders shall email the National Pharmacovigilance Centre at pv@ppb.go.ke or call +254 795 743 040.

iv) Surveys and Questionnaires

The Board shall assess stakeholder experiences and satisfaction with the PV system through structured surveys or questionnaires every two years.

v) Dedicated Communication Channels

The Board shall maintain dedicated PV communication channels where stakeholders provide feedback on regulatory processes, safety concerns, or challenges in compliance. The communication channels available for providing feedback to the National Pharmacovigilance Centre shall include;

Email: pv@ppb.go.ke

Phone : +254 795 743 040

Social Media pages: X: @ppbkenya

Facebook: Pharmacy and Poisons Board

4. GUIDE TO REPORTING ADVERSE EVENTS

4.1. Who should report AEs?

Reporters may be from the public or private health sector. They include all healthcare providers including medical doctors, dentists, pharmacists, clinical officers, pharmaceutical technologists and nurses. Other reporters include public health professionals, staff in medical laboratories, community healthcare professionals, pharmaceutical manufacturing companies, marketing authorization holders (MAHs), local technical representatives (LTRs) and parallel importers. Patients or patient representatives/guardians and the general public are also encouraged to report.

Submission of a report does not constitute an admission that the medical personnel or manufacturer or the product caused or contributed to the event.

Any information on the reporter and patient identities shall be kept CONFIDENTIAL and shall not be disclosed in response to any public request. In addition, no reporter shall be penalized for reporting on the ADRs including medication errors.

It is important that any ADR or AE is reported even when not certain about the suspected medicine causing the same.

4.2. How to recognize AEs in patients?

The following approach is helpful in assessing possible AEs:

a. Take a proper patient history

b. Establish time relationships by asking if the AEs occurred immediately following the drug administration.

c. **Carry out a thorough physical examination with appropriate laboratory investigations if necessary:**

d. For medicines, check the effect of Dechallenge and Rechallenge should be determined

i. *Dechallenge (withdrawal of the suspected drug)*
Positive dechallenge is the improvement/resolution of ADR when the suspected drug is withdrawn in a strong, though not conclusive indication of drug-induced reaction.

ii. *Rechallenge (re-introducing the suspected drug after a dechallenge*)
Rechallenge is only justifiable when the benefit of reintroducing the suspected drug to the patient outweighs the risk of recurrence of the reaction, which is rare. In some cases, the reaction may be more severe on repeated exposure. Rechallenge requires serious ethical considerations.

e. Check the known pharmacology of the medicine

i. Check if the reaction is known to occur with the particular suspected drug as stated in the package insert or other reference.

ii. **Remember**: If the reaction is not documented in the package insert, it does not mean that the reaction cannot occur with that particular suspected medicine.

4.3. What to report

It is important to report the following:

a. All expected and unexpected suspected ADRs and AEs to conventional medicines, allopathic medicines, traditional/alternative/herbal medicines, biologicals, vaccines, x-ray contrast media, cosmeceuticals, and medical devices, including in vitro diagnostics. This includes both serious and non-serious adverse events;
b. All medication errors;
c. All suspected ADRs and AEs that may be associated with suspected or confirmed quality defects including adulteration or contamination, or substandard and falsified HPTs;
d. Case reports of acute and chronic poisoning (toxicity);
e. Abuse, overdose and misuse of medicines;

f. Adverse interactions of medicines with chemicals, other medicines and food;
g. Lack of therapeutic efficacy/therapeutic failure;
h. All suspected poor-quality HPTs and
i. Any ADRs or AEs observed in pregnancy or during breastfeeding.

4.4. When to report

Any suspected ADR and /or AE shall be reported as soon as possible to the National Pharmacovigilance Centre at the Board. The following timelines for reporting apply to spontaneous cases encountered by healthcare professionals and the patients/ public:

a. Fatal cases - The Board shall be notified immediately and a report submitted within 48 hours.
b. Serious (non-fatal) cases shall be reported within 15 calendar days.
c. Non-serious local cases shall be reported within 30 calendar days.

4.5. How to report a suspected AE

Report a suspected AE using reporting forms (Annexes 1-5) either physically or on the pharmacovigilance electronic reporting system (PvERS) and mobile pharmacovigilance electronic reporting system mPvERS app (mobile application on Play Store and App Store). There are four critical sections to complete:

a. Patient details- provide details such as the patient's name or initials, age or date of birth, gender, pregnancy status (where applicable), allergy status and physical address
b. Details of the adverse event/incident- give a detailed description of the signs and symptoms of the event, date of onset of the event/incident, seriousness classification of the event/incident and outcome of the event/incident at the time of reporting
c. Product/Medical device details- record the name of the product, date of administration/installation, route or site of administration/installation, batch number, expiry date
d. Reporter's details- record the name of the reporter, designation, contact

details, and the date of completion of the form.

4.6. Where to report

For the healthcare professionals, the reporting channels are as follows:

a. Online at the Pharmacovigilance electronic reporting system (PvERS) at www.pv.pharmacyboardkenya.org.
b. mPvERS mobile application for both Android (Play Store) and iOS (App Store).
c. E-mail scanned filled forms or details of the reaction to pv@ppb.go.ke.
d. Manual reporting forms are available at public and private health facilities, while downloadable soft copies are found on the PPB website at www.pharmacyboardkenya.org/pharmacovigilance/. This can be hand delivered, posted or sent through the Board's address as follows:

   Pharmacy and Poisons Board,
   P.O. Box 27663 – 00506, Nairobi, Lenana Road Opp. DOD
   Tel: +254 709770100

e. The **general public/patients**, can report by dialling the **USSD code *271#** and follow the prompts or call, text, or WhatsApp on +254795743049
f. MAHs shall upload the ICH-E2B xml file directly to the PvERS or submit a report by completing the relevant form on the PvERS at www.pv.pharmacyboardkenya.org

4.7. Conducting investigations on HPTs

The County/Sub–County Investigation Team (SCIT) shall be formed on an ad hoc basis and shall comprise members from the Sub-County Health Management Team (SCHMT) and the County vigilance focal person for follow-up of serious ADRs and/or adverse events (AEs) in the respective Sub-counties. Representatives from the National Team (Pharmacy and Poisons Board and/or the relevant Public Health Programs) shall be co-opted in some investigations

The purpose of the investigation is to:

a) Confirm the reported diagnosis and timing of adverse events.

b) Identify details of the suspected health product administered or used.
c) Determine the cause of the reaction or event.
d) Document the outcome of the reported adverse reaction or event.
e) Determine whether the reported reaction or event is a single incident or part of a cluster.

The AEs that require investigation include:

i. Serious AEs reported;
ii. Clusters of AEs;
iii. Occurrence of reactions or events above the expected rate or of unusual severity;
iv. Potential Signals;
v. Events causing significant public health or community concern.

The National Pharmacovigilance Centre shall initiate the investigation of adverse events within 48 hours but not later than 7 days from the receipt of the ICSR. An investigation form (**Annex 10 & 11**) shall be used as a guide during the investigations.

4.8. What happens to the reported AEs?

The reports received at the Board are stored in the national PV database and analysed by expert reviewers on a regular basis. They shall then be forwarded to the WHO-Uppsala Monitoring Centre international database, VigiBase. Feedback on the findings shall be communicated to the reporters (Figures 1 and 2 below).

The safety information obtained from reports sent to PPB shall assist in evidence-based regulatory decision-making towards ensuring the protection of public health and enhanced patient safety. The regulatory decisions include but not limited to:

a. Appropriate changes to the package insert.
b. Scheduling and rescheduling of medicines.
c. Recall or withdrawals.
d. Formulation or change of policies.

Figure 1: What happens to the reported adverse events

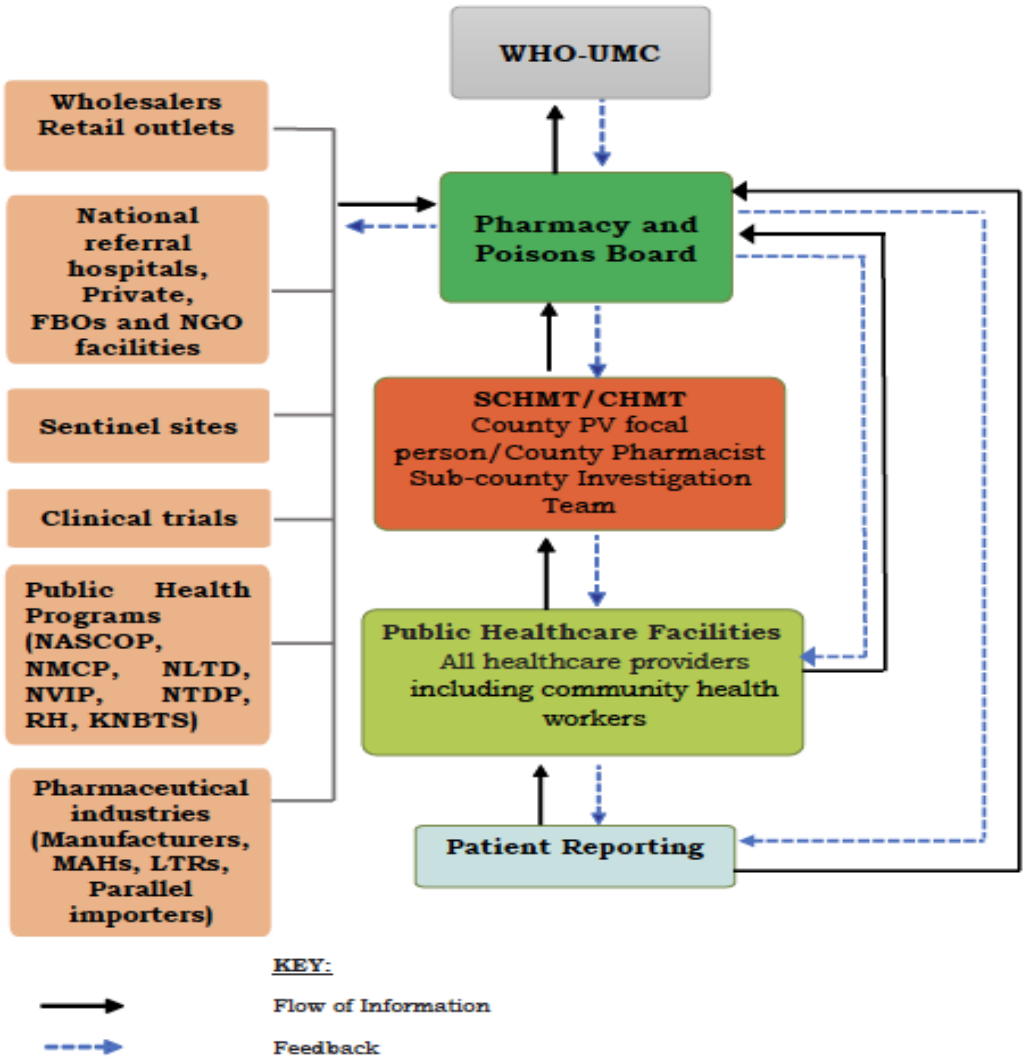

Figure 2: Flow of AE information

5. OBLIGATIONS OF THE HEALTHCARE PROFESSIONALS

The healthcare professionals shall report both serious and non-serious AEs within the timelines prescribed below (and in section 4.3).

a. Fatal cases - The Board shall be notified immediately and a report submitted within 48 hours.
b. Serious (non-fatal) cases shall be reported within 15 calendar days.
c. Non-serious local cases shall be reported within 30 calendar days.

5.1. Adverse Drug Reaction and Side Effects (ADRs)

An ADR is a response to a medicine which is noxious and unintended, and which can occur at doses normally used in humans, such as Sulfamethoxazole/trimethoprim-related Stevens-Johnson Syndrome. ADRs are classified based on the type of reaction, the onset of the event, severity, and seriousness. While the terms ADR and side effect are often used interchangeably, they have distinct differences. A side effect, however, is any expected but unintended effect of a pharmaceutical product that occurs at doses typically used in humans, related to the product's pharmacological properties.

Healthcare professionals should be aware of risk factors that predispose patients to ADRs, such as dosage, polypharmacy, comorbidities, drug-drug interactions, age, pregnancy, and alcohol and substance abuse. By understanding drug and patient-related risk factors, knowing when to suspect an ADR, and reporting suspected reactions through established systems, healthcare professionals can help prevent avoidable situations and keep patients safe.

All ADRs, therapeutic ineffectiveness, off-label use, acute and chronic poisoning (toxicity), use of herbal products, and adverse interactions with other medicines and food shall be reported using the suspected adverse drug reaction reporting form **(Annex 1)** within the prescribed timelines.

5.2. Adverse Events Following Immunization (AEFI)

The WHO defines an AEFI as any untoward medical occurrence, which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

An AEFI can be product related, quality defect-related, immunization error related, immunization anxiety related and coincidental.

Vaccine safety monitoring is a collaborative process that involves the National Vaccines and Immunization Program (NVIP), PPB, healthcare providers, consumers, partners and other stakeholders.

5.2.1. Reporting AEFIs

Health care workers and caregivers shall report both serious and non-serious AEFI cases. These include:

a. Serious AEFIs i.e., adverse events or reactions that result in death, hospitalization (or prolongation of existing hospital stay), persistent or significant disability or incapacity (e.g. paralysis), or are potentially life-threatening;
b. Signals and events associated with a newly introduced vaccine;
c. AEFIs that may have been caused by immunization error (e.g. Injection site abscesses, severe local reaction, high fever or sepsis, BCG toxic shock syndrome, clusters of AEFIs);
d. Allergic reaction- anaphylaxis, hives, bronchospasm, oedema;
e. Clusters of events (> 2 cases of same event in same month) apart from fever;
f. Seizures;
g. Any events causing significant parental/caregiver or community concern;
h. Swelling, redness, soreness at the site of injection **IF** it lasts more than 3 days or swelling extends beyond nearest joint, inability to move the limb.

More examples of AEFI that should be reported in relation to onset time

interval if vaccine is implicated is summarized in Table 1.

A detailed investigation shall thereafter be initiated by trained/skilled persons/teams from both PPB and NVIP at the National and County or sub-county level as soon as possible, ideally within 48 hours of the case being first reported. An AEFI investigation form (**Annex 11**) can be used as a guide during the investigations.

Table 1: AEFIs and their respective onset time interval

***Reportable AEFI**	****Onset time interval if vaccine/vaccination is implicated**
•Anaphylactoid reaction (acute hypersensitivity reaction) •Anaphylaxis •Persistent inconsolable screaming (more than 3 hours) •Hypotonic hypo-responsive episode (HHE) •Toxic shock syndrome (TSS)	Within 24 to 48 hours of immunization
•Severe local reaction •Sepsis •Injection site abscess (bacterial/sterile)	Within 7 days of immunization
•Seizures, including febrile seizures (6-12 days for measles/MMR; 0-2 days for DTP) •Encephalopathy (6-12 days for measles/MMR; 0-2 days for DTP)	Within 14 days of immunization
•Acute flaccid paralysis (4-30 days for OPV recipient; 4-75 days for contact) •Brachial neuritis (2-28 days after tetanus containing vaccine) •Intussusception (commonly within 21 days after rotavirus vaccines) •Thrombocytopenia (15-35 days after measles/MMR)	Within 3 months of immunization
•Lymphadenitis • Disseminated BCG infection • Osteitis /Osteomyelitis	Between 1 and 12 months after BCG immunization
•Death •Hospitalization •Disability •Any other severe and unusual events that are thought by healthcare professionals or the public to be related to immunization	No time limit

**The list of reportable AEFIs is meant as a guide and by no means exhaustive. In general, healthcare workers are advised to report all events following immunization as long as no other clear cause has been identified. This would include events whereby a causal link to a vaccine has not been established.*

***Onset interval is meant as a general guiding principle and will depend on the antigen and adverse reaction, as well as patient factors.*

The National Vaccine Safety Advisory Committee (NVSAC) shall then review all reported serious AEFIs presented to them for expert opinion, conduct

causality assessment, draw conclusions and make recommendations to improve the immunization program and promote the safety of vaccines.

5.3. Haemovigilance of blood and blood products

The WHO defines hemovigilance as a set of surveillance procedures covering the entire blood transfusion chain, from the donation and processing of blood and its components, through to their provision and transfusion to patients, and including their follow-up. Adverse events include all reactions, incidents, near misses, errors, deviations from standard operating procedures and accidents associated with blood donation and transfusion. The Figure 2 below shows the classification of transfusion reactions.

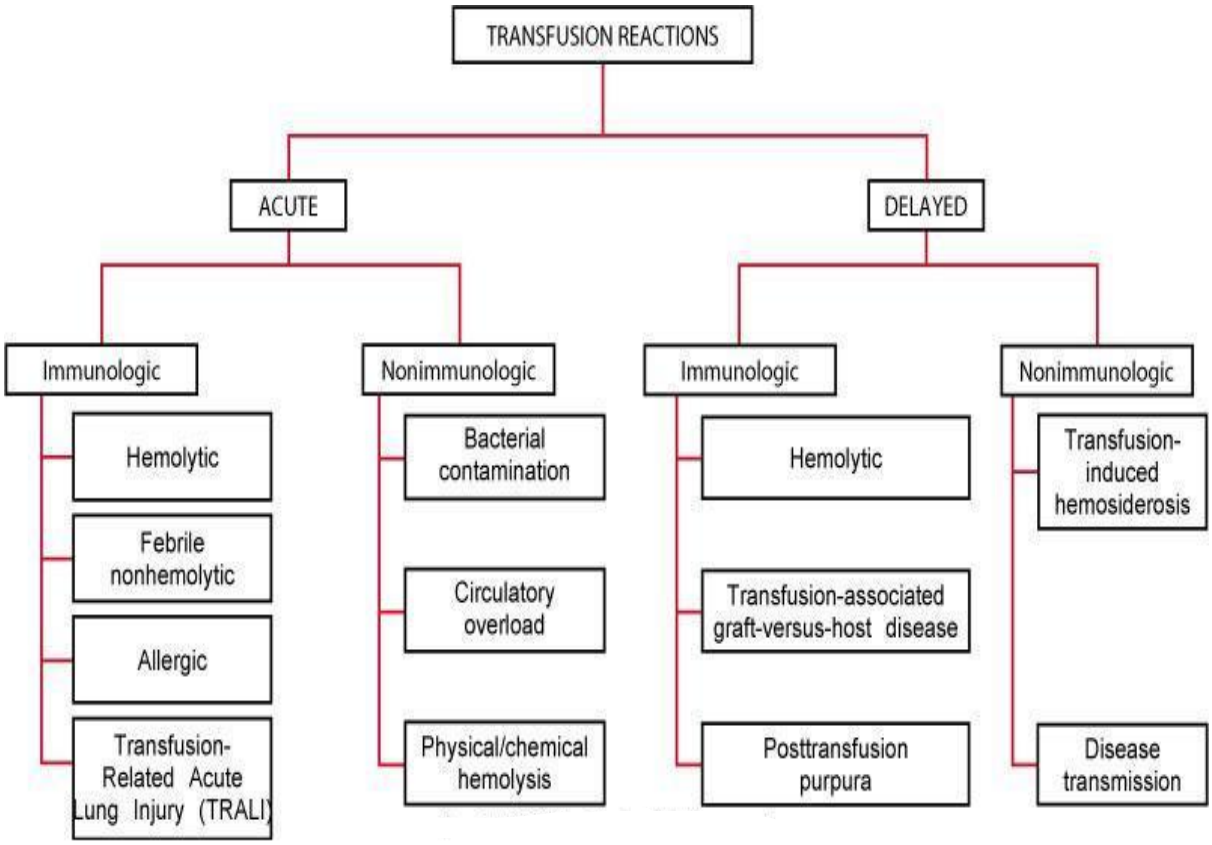

Figure 3: Classification of Transfusion reactions (adapted from Elsevier, 2005)

It involves monitoring, reporting, investigating, and analyzing adverse events related to the donation, processing, and transfusion of blood and acting to prevent their occurrence or recurrence. In this case, the health care providers

shall report using the suspected adverse blood and blood products transfusion reaction reporting form **(Annex 3).**

The clinician shall fill out a transfusion reaction form immediately after the reaction occurs. Similarly, the laboratory technologist who carries out the investigation shall fill out a transfusion reaction register. The Hemovigilance officer shall prepare a hemovigilance report and submit it to the KNBTS. The KNBTS hemovigilance officer shall then forward the reports to PPB.

5.4. Medication Errors

Medication errors are any preventable events that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional or the patient/client. Medication errors can occur during procuring drugs, prescribing, dispensing, or administering. Some of the factors that contribute to medication errors include system factors, human factors, and patient factors. Any medical error shall be reported using the medication errors reporting form **(Annex 5).**

5.5. Reporting suspected adverse events with medical devices including in vitro diagnostics

The safety and performance of medical devices have a great and direct impact on patient safety. Errors, failures, and defects in medical devices, including IVDs, may have serious consequences for patients and healthcare professionals.

An adverse event/incident due to a medical device shall be reported to the manufacturers and the Board. The following three criteria of events shall be reported to the Board:

a. An event has occurred. This may include:
    - A malfunction or deterioration in the characteristics or performance.
    - An incorrect or out of specification test result.

- The discovery of a design flaw during design review.
- An inaccuracy in the labelling, instructions for use and/or promotional materials. Inaccuracies include omissions and deficiencies.
- The discovery of a serious public health threat;
- Use error.

b. The manufacturer's device is associated with the event.

c. The event led to one of the following outcomes:

- Death of patient, user or another person.
- Serious Injury of a Patient, User or Other Person: It may be a life-threatening illness or injury, permanent impairment of a body function or damage to a body structure, a condition necessitating medical or surgical treatment to prevent permanent impairment
- Near incidents: No death or serious injury occurred but the event might lead to death or serious injury of a patient, user or other person if the event recurs.

Any incident, whether the fault is due to technical faults or defects in the equipment, instruction manual, marking, use, or maintenance, must be reported even when in doubt.

All adverse events/ incidents shall be reported to the Board using the medical devices incident reporting form (**Annex 4**). Poor-quality or defective medical devices, including IVDs, shall be reported using the poor-quality reporting form (**Annex 6**).

Conditions where reporting is not required include:

1. Deficiency of a device found by the user prior to its use.
2. Adverse event caused by patient conditions.
3. Service or shelf life of the medical device exceeded.
4. Protection against a fault functioned correctly.
5. Expected and foreseeable side effects.
6. Negligible likelihood of occurrence of death or serious injury.

5.6. Reporting Poor Quality Health Products and Technologies

All healthcare providers in the private and public sectors shall alert PPB on product quality issues. Poor-quality Health Products and Technologies shall be reported as per the Guideline for Post-Marketing Surveillance of Medical Products and Health Technologies in Kenya (HPT/PDS/VMS/GUD/054).

6. OBLIGATIONS OF THE MARKETING AUTHORIZATION HOLDERS

6.1. Submission of individual case safety reports (ICSRs)

The MAHs shall upload the ICH-E2B XML file directly to the PvERS or report directly by completing the relevant form on the PvERS at https://pv.pharmacyboardkenya.org/. The following timelines apply:

a. Local fatal cases shall be reported within 7 calendar days.
b. Serious (non-fatal) cases that have occurred in Kenya shall be reported within 15 calendar days.
c. Non-serious local cases shall be reported within 30 calendar days.
d. All foreign cases, whether serious (including those that are fatal) or non-serious, shall be reported within the Periodic Safety Update Report (PSURs) or Periodic Benefit/Risk Evaluation Report (PBRER) as per prescribed timelines in this guideline.

6.2. Periodic safety update reports

The objective of the PSUR is to present a comprehensive and critical analysis of the product's risk-benefit balance, considering new or emerging safety information in the context of cumulative information on risk and benefits.

The MAHs and manufacturers shall be responsible for ensuring the quality, safety and efficacy of the products they register and/or supply in the Kenyan market. The PSURs shall be prepared and submitted according to the International Birth Date (IBD) for all medicines within the stated timelines as stipulated by the Board.

In addition, any foreign regulatory decisions that affect the safety or use of products marketed, donated, imported, and/or for compassionate use shall

be reported to the Board within 7 calendar days through a detailed report on the same.

It is the responsibility of the QPPV to ensure that PSURs are submitted according to this guideline.
The PSURs must be prepared and submitted by the MAH to the Board by uploading it to the PvERS at https://pv.pharmacyboardkenya.org/ at the following intervals:

1. **Upon request.**
2. **Every 6 months** from authorization until the product is placed in the market.
3. **Every 6 months for the first two years** on the market.
4. **Annually** for the next two years.
5. Thereafter **every 3 years.**

The following timelines apply for the submission of PSURs:

i. Within 70 calendar days of the DLP (Day 0) for PSURs covering intervals of 6 to 12 months.
ii. Within 90 calendar days of the DLP (Day 0) for PSURs covering intervals in excess of 12 months.
iii. Ad hoc PSURs shall be submitted upon request within 90 calendar days of the DLP, unless otherwise specified.

The PSURs shall emphasize on the following:

a. Scientific evaluation of the benefit-risk profile.
b. Summaries of relevant scientific/clinical data including literature searches.
c. In addition, please include an executive summary of any changes that may have occurred from the last submission. Classify whether these changes are major or minor. The format of the executive summary is below:

	Previous status	**Current changes**	**Section/Page**	**Classification of changes (major or minor)**
1				
2				

Please note that the reaction terms used in the report shall be in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

6.3. Periodic Benefit-Risk Evaluation Reports

The main objective of a Periodic Benefit-Risk Evaluation report (PBRER) is to present a comprehensive, concise, and critical analysis of new or emerging information on the risks of the medical product, and on its benefits in approved indications, to enable an appraisal of the product's overall benefit-risk profile.

6.3.1. Scope

The use of a single harmonised IBD and DLP for each product is also permissible to reduce the burden of work involved in preparing PBRERs. The MAH may, therefore, submit a PSUR/PBRER according to the EU reference dates (EURD) list.

The PBRER shall contain an evaluation of new information relevant to the medical product that has become available to the MAH during the reporting interval, in the context of cumulative information by:

1. Summarizing relevant new safety information that could have an impact on the benefit- risk profile of the health product.
2. Summarizing any important new efficacy/effectiveness information that has become available during the reporting interval.
3. Examining whether the information obtained by the MAH during the reporting interval is in accord with previous knowledge of the medical product's benefit and risk profile.
4. Where important new safety information has emerged, conducting an integrated benefit- risk evaluation for approved indications.

When appropriate, the PBRER shall include proposed action(s) to optimize the benefit-risk profile. The PBRER shall be prepared in the format prescribed in the Annex (Reference No) and shall contain the following minimum requirement;

i. Summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorization;
ii. A scientific evaluation of the risk-benefit balance of the medicinal product;
iii. All data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorization holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product;
iv. Collection of Adverse Drug Reaction (ADR) information (i.e., local serious ADRs, local non-serious ADRs, foreign serious ADRs, foreign non-serious ADRs, case reports published on international or local literatures including academic conferences);
v. A comprehensive, concise, and critical analysis of product's known or emerging important risks and to evidence of emerging important benefits including the following;
vi. Summary of relevant new safety information that could have an impact on the benefit-risk profile of the product;
vii. Summary of any important new efficacy/effectiveness information that has become available during the reporting interval;
viii. Assessment of whether the information obtained by the MAH during the reporting interval is in accord with previous knowledge of the product's benefit and risk profile;
ix. Conducting an integrated benefit-risk evaluation for approved indications in case a new safety information that has emerged;
x. Recommend action(s) to optimize the benefit-risk profile.

6.3.2. General Principles

A. Single PBRER for an Active Substance

The PBRER shall provide information on all approved indications, dosage forms and regimens for the active substance with a single DLP. In exceptional cases, for example where an active substance has been used in two

formulations, for systemic and topical administration with entirely different indications, separate PBRERs shall be submitted.

B. PBRERs for Fixed-Dose Combination Product

For combinations of substances also marketed individually, information for the fixed combination can be reported either in a separate PBRER or included as separate presentations in the report for one of the individual substances, depending on the circumstances. Listing related PBRERs is considered important.

C. Products Manufactured and/or Marketed by More Than One Company

Each MAH and any other entity/company responsible for marketing and /or importation of health products for use in the Kenyan market is responsible for submitting PBRERs for their own products.

When companies are involved in contractual relationships (e.g., licensor-licensee), respective responsibilities for preparation and submission of the PBRER to the Board shall be clearly specified in the written agreement. When data received from a partner company(ies) might contribute meaningfully to the safety, benefit, and/or benefit-risk analyses and influence the reporting company's product information, these data shall be included and discussed in the PBRER.

D. Benefit-Risk Evaluation

Benefit-risk evaluation shall be carried out to determine whether benefits continue to outweigh risks, and to consider whether steps should be taken to improve the benefit-risk balance through risk minimization activities (e.g., labelling changes, communications with prescribers, or other steps).

The QPPV shall submit PBRERs as prescribed in the current ICH Guideline E2C on PBRER, by uploading it to the PvERS at pv.pharmacyboardkenya.org as per the following timelines;

1. **Upon request.**
2. **Every 6 months for the first two years** after marketing authorization;

within 70 calendar days.

3. **Annually for the next two years;** within 90 calendar days.
4. **Thereafter every three years** for products that have been marketed for several years and considered to have an established and acceptable profile or considered to be low risk; within 90 calendar days.

The MAH shall continuously evaluate whether any revision of the reference product information/Reference Safety Information (RSI) is needed whenever new safety information is obtained throughout the reporting interval. Significant changes to the reference product information/RSI made during the interval shall be described in the executive summary. The format for the executive summary is as described in section 7.2 (PSUR).

i. Changes to contraindications, warnings/precautions sections of the RSI;
ii. Addition of Adverse Drug Reaction(s) (ADR) and interactions;
iii. Addition of important new information on use in overdose; and
iv. Removal of an indication or other restrictions for safety or lack of efficacy reasons.

6.4. Risk Management Plans (RMPs)

The aim of a Risk Management Plan (RMP) is to document the risk management system (RMS) considered necessary to identify, characterize and minimize a health product's important risk.

6.4.1. General principles of risk management

1. The MAH shall have RMPs for their health products throughout their lifecycle. The RMS shall be proportionate to the identified risks and the potential risks of the health products and technologies the need for post-authorization safety data.

2. The RMP is a dynamic document that shall be updated throughout the life cycle of the product(s). This includes the addition of safety concerns where required, but also, as the safety profile is further characterized, the removal or reclassification of safety concerns to include new concerns.

3. The removal of safety concerns in the RMP shall be under the following circumstances:
   i. Removal of a safety concern for important potential risks:
      a. Accumulating scientific and clinical data do not support the initial supposition, or the impact to the individual has been shown to be less than anticipated.
      b. When there is no reasonable expectation that any pharmacovigilance activity can further characterise the risk.
   ii. Removal of a safety concern for important identified risks:
      a. In certain circumstances, where the risk is fully characterised and appropriately managed (e.g., for products marketed for a long time for which there are no outstanding additional pharmacovigilance activities and/or the risk minimisation activities have become fully integrated into standard clinical practice such as inclusion into treatment protocols or clinical guidelines.
   iii. Removal of a safety concern for missing information:
      a. The missing information might not be appropriate anymore once new data become available, or when there is no reasonable expectation that further feasible PV activities could further characterise the safety profile,

4. The risk management system shall be proportionate to the identified risks and the potential risks of the medicinal product, and the need for post-authorization safety data.

6.4.2. Risk management plan format

The MAH shall prepare and submit to the Board an RMP in the format as prescribed in **annex 13** at pv@ppb.go.ke. It shall contain the following:

a. Safety Specifications: identification or characterization of the safety profile of the medical product and/or the health technology, with emphasis on important identified and important potential risks and missing information, and also on which safety concerns need to be managed proactively or further studied (the 'safety specification');
b. Pharmacovigilance plan: Planning of pharmacovigilance activities to

characterise and quantify clinically relevant risks, and to identify new adverse reactions;

c. Risk minimisation plan: Planning and implementation of risk minimisation interventions (RMI), including the evaluation of the effectiveness of these activities.

The RMP document shall be submitted as one single document including all sections and annexes, as relevant. The following applies:

1. Where applicable, the information in the RMP shall provide an integrated overview/ discussion focusing on the most important risks that have been identified or are anticipated based on pre-clinical, clinical and post-marketing data presented in other modules of the eCTD.
2. Any data included in the RMP shall be consistent with other sections of the dossier. Links or references to relevant sections of the non-clinical and clinical overviews and summaries shall be included in the RMP.
3. For new RMP submissions for authorized products with limited safety data in the dossier, the RMP may contain the relevant safety data and discussion.
4. The preliminary section of the RMP shall include the following administrative information about the RMP document:
   i. Data lock point of the current RMP;
   ii. Sign off date and the version number of the RMP;
   iii. List of all parts and modules. For RMP updates, modules version number and date of approval (opinion date) should be tabulated in this section. High level comment on the rationale for creating the update should be included for significant changes to each module;
   iv. The evidence of oversight from the qualified person for pharmacovigilance (QPPV) is not needed for versions submitted for assessment.
5. **Table *2*** Indicates where information from the eCTD is likely to be discussed in the RMP. The eCTD data refers to the submission containing the RMP (e.g., initial marketing authorization applications and major variations) or to historical data already included in the dossier with previous

submissions.

6. The QPPV's actual signature or the evidence that the RMP was reviewed and approved by the QPPV shall be included in the finalized approved version of the document; The evidence of QPPV oversight can take the form of a statement that the RMP has been reviewed and approved by the marketing authorization holder/applicant's QPPV and that the electronic signature is on file.

Table 2: Mapping between RMP modules and information in eCTD

RMP	**eCTD**
Part I Active substance information	Module 2.3 Quality overall summary Module 3 Quality
Part II Safety specification Module SI Epidemiology of the indication and target population	Module 2.5 Clinical overview Part IV (SMPC)*
Module SII Non-clinical part of safety specification	Module 2.4 Non-clinical overview Module 2.6 Non-clinical written and tabulated summaries Module 4 Non-clinical study reports
Module SIII Clinical trial exposure	Module 2.7 Clinical summary briefly Module 5 Clinical Study reports
Module SIV Populations not studied in clinical trials	Module 2.5 Clinical overview
Module SV Post authorization experience	Module 2.5 Clinical overview briefly
Module SVII Identified and potential risks	Module 2.5 Clinical overview (including benefit risk conclusion) Module 2.7 Clinical summary Part IV (SmPC)*
Module SVIII Summary of the safety concerns	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part III Pharmacovigilance activities	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part IV Plans for post authorization efficacy studies (including presentation of efficacy data)	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part V Risk minimization measures	Module 2.5 Clinical overview Module 2.7 Clinical summary

**Guidelines on medicines evaluation and registration (PPB/PER/MED/GUD/016)*

6.4.3. Kenya Specific Annex to the global RMP

Where an existing global RMP or EU-RMP submitted does not apply to the Kenyan setting, the MAH shall also include the Kenya-specific Annex to it. In cases where there is no difference in the global activities, a signed declaration shall be provided. The Kenya Specific Annex shall provide specific information that is important in assessing the 'risk' in Kenya (and therefore the appropriateness of proposed plans/activities), the relevance of pharmacovigilance and risk minimization activities in Kenya, and identify and explain the reasons for any differences with activities planned in the EU.

6.4.4. Format for the Kenya Specific Annex

The Kenya Specific Annex shall be submitted in the following format:

i. **Introduction** - Purpose of the Kenya Specific Annex.

ii. **Pharmacovigilance plan –** Routine pharmacovigilance practices in Kenya and studies referenced in the RMP. Describe the involvement of Kenya and the applicability of global studies to the Kenyan environment/population, or if not applicable or relevant to the Kenyan environment, include a justification.

iii. **Risk minimization plan –** Address how risk minimization activities will be implemented and evaluated in Kenya. If surveys or studies are referenced in the Kenya Specific Annex copies of protocols should be provided. Provide a justification if activities in the EU are not to be implemented in Kenya. Indicate how and when evaluation of risk minimization activities, including educational activities, shall be undertaken. Marketing Authorization Holders are responsible for showing that the measures they are using to mitigate risk are working and, if not, what actions they shall take to ensure effectiveness.

iv. **Contact person for RMP-** The qualified person for Pharmacovigilance shall be responsible for the implementation of the RMP activities in Kenya.

All RMPs submitted shall be accompanied by a declaration signed by the QPPV (**Annex 13**). The declaration shall indicate that the QPPV has read the

RMP and will ensure implementation of all activities outlined in the RMP.

6.4.5. Risk minimization measures

Risk minimization measures may consist of routine risk minimization or additional risk minimization measures. Safety concerns of a health product are normally adequately addressed by routine risk minimization measures in the risk management plan. In exceptional cases however, routine risk minimization measures will not be sufficient for some risks and additional risk minimization measures shall be necessary to manage the risk and/or improve the risk-benefit balance of a health product.

The MAHs through the QPPV shall submit RMPs to the Board for all new chemical entities or new medicine combinations, biologics and biosimilars in addition to the following conditions:

1. At the time of application for marketing authorization.
2. At the request of the Board whenever there is a concern about a risk affecting the benefit-risk balance of a medicine.
3. When an important pharmacovigilance or risk-minimization milestone has been achieved.
4. When there are changes to the safety specifications or risk management system.

6.5. Safety and vigilance of medical devices including in-vitro diagnostics (IVDs)

The manufacturer shall establish, document and maintain throughout the life-cycle an ongoing process for identifying hazards associated with a medical device, estimating and evaluating the associated risks, controlling these risks, and monitoring the effectiveness of the controls as described in the current ISO 14971:2007-Medical Device Risk Management Standard. In addition, the manufacturer shall establish and maintain an appropriate Quality Management System (QMS) aligned with the specifications in ISO 13485:2016 Medical devices Quality management systems – Requirements for regulatory purposes.

6.5.1. Reporting of adverse events

1. The manufacturer shall either directly or through its authorized

representative, report to the Board the adverse events associated with medical devices that have occurred in Kenya. An adverse event due to a medical device that meets the following three criteria shall be reported to the Board:

a. An event has occurred. This may include:
    i. A malfunction or deterioration in the characteristics or performance;
    ii. An incorrect or out of specification test result;
    iii. The discovery of a design flaw during design review;
    iv. An inaccuracy in the labelling, instructions for use and/or promotional materials. Inaccuracies include omissions and deficiencies;
    v. The discovery of a serious public health threat; and
    vi. Use error.
b. The manufacturer's device is associated with the event.
c. The event led to one of the following outcomes:
    i. Death of patient, user or another person;
    ii. Serious injury of a patient, user or other person: it may be life-threatening illness or injury, permanent impairment of a body function or damage to a body structure, a condition necessitating medical or surgical treatment to prevent permanent impairment;
    iii. Near incidents- no death or serious injury occurred but the event might lead to death or serious injury of a patient, user or other person if the event recurs.

2. Adverse events that result in unanticipated death or unanticipated serious injury or represent a serious public health threat must be reported to the Board immediately and not later than 2 calendar days after awareness by the manufacturer.
3. Incidents which occurred outside Kenya and do not lead to a FSCA relevant to Kenya do not need to be reported.
4. The manufacturer shall conduct investigation of serious events and submit the investigation reports to the Board as soon as possible but not later

than 15 days. The Board shall monitor the progress of investigations conducted.

5. All other reportable events must be reported as soon as possible by the manufacturer, but not later than 30-elapsed calendar days following the date of awareness of the event.
6. All serious and non-serious incidents/events that have occurred in Kenya shall be reported to the Board using the medical devices incident reporting form (**Annex 4**) at https://pv.pharmacyboardkenya.org/.
7. Manufacturers may be required to review and to revise labelling information (including precautions and warnings), especially for products that have been found to be associated with adverse events or those whose labelling has been shown to be inadequate.
8. The manufacturer shall directly, through the authorised representative, have primary responsibility for notifying users of problems with a medical device.
9. The Board shall also notify the HCPs on serious adverse incidents and FSCA by issuing safety alerts and advisories.
10. The Board shall employ reliance and recognition mechanisms on safety related issues for medical devices including IVDs

6.5.2. Field Safety Corrective Actions (FSCAs) and Field safety Notices (FSNs)

1. The manufacturer shall report to the PPB in a timely manner, either directly or through its authorised representative, any Field Safety Corrective Actions it is undertaking within the country.
2. Field Safety Notices (FNA) and Field Safety Corrective Actions (FSCA), including those based on incidents occurring outside Kenya, shall be submitted to the Board in periodic summary reports. The reports shall include the full details of vigilance issues, including the status of any FSCAs or Notices. They shall be completed using the current version of the WHO FSCA and FSN reporting template (Annexed).
3. The MAH shall disseminate the FSN ensuring that all the relevant stakeholders have been informed after obtaining approval from the Board.

4. The Board may request that the MAH conduct a concise critical analysis of the medical device or IVD's safety and performance and submit results within a specified time frame.
5. The regulatory actions taken by the Board may include recalling the device, reclassifying it, or ordering a redesign from the manufacturer or another.

6.5.3. Risk management

1. Risk management activities shall begin as early as possible in the design and development phase when it is easier to prevent problems.
2. After the device is released to market, risk management activities shall be linked to quality management processes, such as production and process controls, corrective and preventive actions (CAPA), servicing, and customer feedback.
3. Risk management plan.

a. Risk management planning shall be in the span of the entire life cycle of a device. The plan shall include the following:
    i. Scope of the plan, device and the life cycle phases
    ii. Design development process
    iii. Risk management activities and methods
    iv. Verification plan for risk control measures
    v. Reviews
    vi. Allocation of responsibilities
    vii. Criteria for risk acceptability
b. The following risk management activities shall be included in the plan;
    i. Establishment of risk acceptability criteria
    ii. Risk analysis
    iii. Hazard Identification
    iv. Risk analysis methods
c. The following tools shall be considered for analysis and validation risk management;
    i. Preliminary Hazards Analysis (PHA)
    ii. Fault Tree Analysis (FTA)
    iii. Failure Mode Effect Analysis (FMEA)
    iv. Failure Mode Effect and Criticality Analysis (FMECA)

v. Hazard and Operability Study (HAZOP)
vi. Hazard Analysis and Critical Control Point (HACCP)
vii. Risk evaluation including; Risk benefit analysis, Assessment of risks and Assessment of benefits.
viii. Risk control and monitoring

4. Strategies to control or mitigate risks of use-related hazards shall include but not limited to the following:
   i. Modify device design to remove hazard or reduce its consequences:
   ii. Make user interface, including operating logic, error tolerant (safety features):
   iii. Alert users to the hazard.
   iv. Develop written procedures and training for safe operation.
   v. Determine if the risks related to device use are acceptable and determine if new hazards have been introduced.
   vi. Demonstrate safe and effective device use (validation).

5. Documentation of Risk management activities.
   Documents or records resulting from risk management activities such as risk management procedures, reports, etc. shall be maintained or referenced in either a risk management file or other appropriate files (e.g., Design History File, Technical File/Technical Documentation, Design Dossier, Device Master Record, Device History Record, or Process Validation file.

6.6. Pharmacovigilance system master file (PSMF)

The objective of the Pharmacovigilance system master file (PSMF) is to provide an overview of the pharmacovigilance system, which may be requested and assessed by the Board during marketing authorization application(s) or post market authorization. It shall also contribute to the appropriate planning and conduct of audits by the applicant or marketing authorizations holder(s), the fulfilment of supervisory responsibilities of the QPPV, and of inspections or other verification of compliance by the Board. The format and layout of the PSMF is outlined in **Annex 14**.

Through the development and maintenance of the PSMF, the marketing

authorization holder and the QPPV shall be able to:

i. Gain assurance that a pharmacovigilance system has been implemented in accordance with the requirements;
ii. Confirm aspects of compliance in relation to the system;
iii. Obtain information about deficiencies in the system, or non-compliance with the requirements;
iv. Obtain information about risks or actual failure in the conduct of specific aspects of pharmacovigilance.

Pharmaceutical companies including the MAHs, LTRs (where the MAH is not within Kenya) and parallel importers shall be required to maintain and make available a pharmacovigilance system master file (PSMF) upon request by the Board.

1. The PSMF shall be located either at the site where the main pharmacovigilance activities of the MAH are performed or at the site where the qualified person responsible for pharmacovigilance operates.

2. The PSMF shall be continuously accessible to the QPPV and to the Board on request. The information shall be concise, accurate and reflect the current system in place, which means that whatever format is used, it must be possible to keep the information up to date and, when necessary, to revise to take account of experience gained, technical and scientific progress and amendments to the legislative requirements.

3. Marketing authorization holders should be aware that immediate access to the PSMF may also be required by the Board, at the stated PSMF location or QPPV site (if different).

4. The MAH shall maintain both the global PSMF (which follows the EMA format) and the sub-system which describes key elements of PV activities in Kenya both permanently and readily available to the QPPV and the Board at request.

5. The PSMF shall describe the pharmacovigilance system for one or more health products of the MAH. For different categories of health products, the MAH may, if appropriate, apply separate pharmacovigilance systems. Each such system shall be described in a separate addendum within the PSMF.

6. Where a single MAH establishes more than one pharmacovigilance system e.g., specific systems for particular types of products (vaccines, consumer health, etc.), or that the pharmacovigilance system may include products from more than one MAH, a specific PSMF shall be in place to describe each system. A single QPPV shall be appointed to be responsible for the establishment and maintenance of the pharmacovigilance system described in the PSMF.

7. Where a pharmacovigilance system is shared by several MAHs each MAH is responsible for ensuring that a PSMF exists to describe the pharmacovigilance system applicable for their products. For a particular product(s) the MAH may delegate through written agreement (e.g., to a licensing partner or contractor) part or all of the pharmacovigilance activity for which the MAH is responsible.

8. In this case, the PSMF of the marketing authorization holder may cross refer to all or part of the PSMF managed by the system of the party to whom the activity has been delegated subject to agreement on access to that system's information for the MAH and the authorities. Where applicable, a list of all PSMFs held by the same MAH holder shall be provided in the annex, this includes their location(s), details of the responsible QPPV(s) and the relevant product(s). Submission of summary information to the Board cannot contain multiple locations for a single PSMF.

9. When delegating any activities concerning the pharmacovigilance system and its master file, the MAH shall retain the ultimate

responsibility for the pharmacovigilance system, submission of information about the PSMF location, maintenance of the PSMF and its provision to the Board upon request. Detailed written agreements describing the roles and responsibilities for PSMF content, submissions and management, as well as to govern the conduct of pharmacovigilance in accordance with the legal requirements, should be in place.

10. When a pharmacovigilance system is shared, it is advised that the partners agree on how to mutually maintain the relevant sections within their own PSMFs. Accessibility of the PSMF to all the applicable MAH(s), and its provision to the Board should be defined in written agreements. It is vital that MAH(s) can gain assurance that the pharmacovigilance system used for its products is appropriate and compliant.

11. The PSMF shall be kept up to date and be permanently available to the QPPV. It shall also be permanently available for inspection, at the site where it is kept, irrespective of whether the inspection has been notified in advance or is unannounced.

12. The marketing authorization holder shall maintain and make available a copy of the PSMF on request. The copy must be submitted no later than 7 days after the Board's request. It shall be submitted in readable electronic format or a clearly arranged printed copy.

6.6.1. Document and record control

1. The PSMF shall contain a general description of the types of documents used in pharmacovigilance (standards, operating procedures, work instructions, etc..), the applicability of the various documents at the global, regional or local levels within the organization, and the controls that are applied to their accessibility, implementation and maintenance.

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

3. A list of specific procedures and processes related to the pharmacovigilance activities and interfaces with other functions, with details of how the procedures can be accessed, must be provided and detailed guidance.

6.6.2. Audit

4. Information about quality assurance auditing of the pharmacovigilance system shall be included in the PSMF.
5. A description of the approach used to plan audits of the pharmacovigilance system and the reporting mechanism and timelines shall be provided, with a current list of the scheduled and completed audits concerning the pharmacovigilance system maintained in the annex. This list shall describe the date(s) (of conduct and of report), scope and completion status of audits of service providers, specific pharmacovigilance activities or sites undertaking pharmacovigilance and their operational interfaces and cover a rolling 5-year period.
6. The PSMF shall also contain a note associated with any audit where significant findings are raised. The audit report must be documented within the quality system; in the PSMF it is sufficient to provide a brief description of the corrective and/or preventative action(s) associated with the significant finding, the date it was identified and the anticipated resolution date(s), with cross reference to the audit report and the documented corrective and preventative action plan(s),the PSMF shall also describe the process for recording, managing and resolving deviations from the quality system; pharmacovigilance procedures, their impact and management until resolved.
7. Audit trail shall also allow traceability of how validated signals have been investigated.

6.6.3. Marketing authorization and maintenance

1. A summary of the applicant's pharmacovigilance system shall be included in the marketing authorization application, which shall include the following in the dossier:
   i. Proof that the applicant has a designated qualified person responsible for pharmacovigilance;
   ii. The contact details of the qualified person;
   iii. A statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities;
   iv. A reference to the location where the PSMF for the medicinal product is kept; and
   v. Pharmacovigilance plan.

2. The pharmacovigilance system may change with time. Changes of activities concerning the master file shall be documented and managed to ensure that the marketing authorization holder fulfils their responsibilities. Changes to the PSMF shall be notified to the PPB. The types of changes that shall be routinely and promptly notified to the Board are:
   i. Updates to the PSMF or its location that are notified to the Board;
   ii. The addition of corrective and/or preventative actions to the PSMF (e.g., following audits and inspections);
   iii. Changes to content that fulfil the criteria for appropriate oversight of the pharmacovigilance system (in terms of capacity, functioning and compliance);
   iv. Changes in arrangements for the provision of the PSMF to the Board;
   v. Transfer of significant services for pharmacovigilance to a third party (e.g., outsourcing of PSUR production);
   vi. Inclusion of products into the pharmacovigilance system for which the QPPV is responsible;
   vii. Changes for existing products which may require a change or increased workload in relation to pharmacovigilance activity e.g. new indications, studies or the addition of regions.
3. Following the transfer of responsibilities, the recipient QPPV shall

explicitly accept the transfer of responsibility for a pharmacovigilance system in writing. The QPPV shall be in a position to ensure and verify that the information contained in the PSMF accurately and up to date reflects the pharmacovigilance system under his/her responsibility.

4. The MAHs shall submit information about important changes to the pharmacovigilance system including:
   i. Changes to the pharmacovigilance safety database(s), which could include a change in the database itself or associated databases, the validation status of the database as well as information about transferred or migrated data;
   ii. Changes in the provision of significant services for pharmacovigilance, especially major contractual arrangements concerning the reporting of safety data;
   iii. Organisational changes, such as takeovers, mergers, changes in the sites at which pharmacovigilance is conducted, or the delegation/transfer of PSMF management.
   iv. Changes to the PSMF shall be recorded so that a history of changes is available (specifying the date and the nature of the change). Changes to the PSMF must be recorded in the logbook. A record of the date and nature of notifications of the changes made available to the competent authorities, the QPPV, and relevant third parties shall be kept to ensure that change control is fully implemented.
   v. The PSMF provides a description of the pharmacovigilance system at the current time as a basis for audits and inspections, but the functioning and scope of the system in the past may need to be understood.

6.7. Case reports from published scientific literature

The authorized representative or MAH shall report published suspected adverse events related to the active substance(s) of their health product and technologies, occurring in Kenya. A copy of the relevant published article shall be provided.

The adverse event report shall be completed for each identifiable patient (with

an identifiable adverse drug reaction) and submitted to the Board in e2b format on the PvERS at https://pv.pharmacyboardkenya.org/.

If more than one medicine is mentioned in the literature report, only the MAH whose medicine is suspected of being the cause is required to submit a report. The suspect medicine is usually the one stated as such in the body or title of the article by the author(s).

6.8. Post-Authorization Studies

The Board shall require MAHs to conduct post-authorization studies on safety and efficacy as a condition of granting the marketing authorization or later. The obligation shall be notified in writing and shall include the objectives and timeframe for the submission and conduct of the study. The request may also include recommendations on key elements of the study (e.g., study design, setting, exposure(s), outcome(s), and study population).

6.8.1. Post-Authorization Safety Studies (PASS)

A post-authorization safety study (PASS) is any study relating to an authorized HPT conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile, or of measuring the effectiveness of risk management measures.

A PASS may be interventional or non-interventional. This guideline's main focus is on non-interventional studies. If a PASS is interventional, then the Guidelines for conduct of clinical trials in Kenya shall be applicable

a) **General Requirements**

A marketing authorization may be granted subject to the conduct of a PASS. The need for a PASS could be identified by the Board during a post authorization procedure, for example, an extension or a variation to a marketing authorization, a renewal procedure or a PSUR procedure.

1. The non-interventional PASS can be imposed due to the following concerns;
   i. imposed as an obligation in accordance with Risk Management Plans stipulated in this guideline because they are key to the risk-benefit

profile of the product (Category 1 studies in the pharmacovigilance plan);

ii. Imposed as a specific obligation in the framework of a marketing authorization granted under exceptional circumstances (Category 2 studies in the pharmacovigilance plan);

iii. Required in the risk management plan (RMP) to investigate a safety concern or to evaluate the effectiveness of risk minimization activities (Category 3 studies in the pharmacovigilance plan). Such studies included in the pharmacovigilance plan are also legally enforceable.

2. A study shall be classified as a post-authorization safety study when the main aim for initiating the study includes any but not limited to the following objectives:

   i. To 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 medicinal product or class of medicinal;

   ii. Products as appropriate, and investigate risk factors, including effect modifiers;

   iii. To evaluate the risks of a medicinal product used in a patient population for which safety information is limited or missing (e.g., pregnant women, specific age groups, patients with renal or hepatic impairment or other relevant comorbidity or co-medication);

   iv. To evaluate the risks of a medical product after long-term use;

   v. To provide evidence about the absence of risks;

   vi. To assess patterns of drug utilization that add knowledge regarding the safety of the medicinal product or the effectiveness of a risk management measure (e.g., collection of information on indication, off-label use, dosage, co-medication or medication errors in clinical practice that may influence safety, as well as studies that provide an estimate of the public health impact of any safety concern);

   vii. To measure the effectiveness of risk management measures.

3. The classification of a post-authorization study as a PASS is not constrained by the type of design chosen. For example, a systematic

literature review or a meta-analysis may be considered as PASS depending on its aim.

4. The Market Authorization Holder shall develop study protocols, the conduct of studies and the writing of study reports by considering relevant scientific guidance.

6.8.2. Post-Authorization Efficacy Studies (PAES)

These studies aim to enhance the understanding of therapeutic efficacy and the benefit-risk of a medicine with implications for better use in clinical practice.

The PAES may be conducted by MAHs under the following circumstances:

a. Uncertainties concerning benefits stemming from (sub)-populations.
b. Uncertainties concerning benefits stemming from endpoints.
c. Uncertainties regarding benefits of treatment over time.
d. Uncertainties in benefits regarding co-treatment with other products.
e. Uncertainties stemming from benefits of the medicinal product in real life use.
f. Change in the understanding of the disease or drug.
g. Change in scientific factors for previous efficacy evaluations.

6.8.3. Application procedure for PASS and PAES

1. The MAH shall develop a study protocol as per the prescribed format in **annex 15** of these guidelines.
2. The qualified person responsible for pharmacovigilance (QPPV) or his/her delegate shall be actively involved in the development, review, and sign-off of study protocols to ensure compliance of the marketing authorization holder with its pharmacovigilance obligations.
3. The QPPV shall submit to the Board about the non-interventional PASS or PAES through pv@ppb.go.ke by sending a cover letter, study protocol (as per Annex 15 format), and Informed consent form (English, Swahili and local languages to be used).
4. The QPPV shall be required to state in the cover letter that the study is PASS or PAES and provide justification as to why it is not a clinical trial.

5. A relevant expert committee (PERAC or NVSAC) shall review the study protocol and approve, reject, or request for additional information.
6. The decision of the expert committee shall be communicated in writing to the applicant within 30 working days of the receipt of a complete and valid application.
7. In the case of rejection, the applicant may appeal and provide additional information to satisfy the expert committee's requirements.
8. Information on studies conducted pursuant to an obligation imposed by the Board shall be included in the risk management plan.
9. Pre-submission meetings might be requested by MAHin order to clarify specific aspects of the requested study and to facilitate the development of the protocol in accordance with the objectives.
10. The Board shall from time to time conduct its own post marketing surveillance studies if deemed relevant to determine safety, quality and effectiveness of the products placed on the market.

6.8.4. Study conduct

1. The study shall commence only when written authorization from the Board has been issued.
2. The studies shall be initiated, managed or financed by a marketing authorization holder voluntarily or pursuant to imposed obligations by the Board.
3. The marketing authorization holder shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified.
4. The code of conduct shall address;
    i. Rationale, main objectives and brief description of the intended methods of the research to be carried out by the investigator(s);
    ii. Rights and obligations of the investigator(s) and marketing authorization holder;
    iii. Clear assignment of tasks and responsibilities;
    iv. Procedure for achieving agreement on the study protocol;
    v. Provisions for meeting the marketing authorization holder's

pharmacovigilance obligations, including the reporting of adverse reactions and other safety data by investigators, where applicable;

vi. Intellectual property rights arising from the study and access to study data;

vii. Storage and availability of analytical dataset and statistical programs for audit and inspection;

viii. Communication strategy for the scheduled progress and final reports;

ix. Publication strategy of interim and final results.

5. The marketing authorization holder shall ensure that the investigators are qualified by education, training and experience to perform their tasks.
6. Agreements between the marketing authorization holder and the investigators shall follow the Board's contractual requirements.
7. Non-interventional post authorization studies shall not be performed where the act of conducting the study promotes the use of a medical product. This requirement applies to all studies and to all activities performed in the study, including for studies conducted by the personnel of the marketing authorization holder and by third parties on behalf of the marketing authorization holder.
8. Payments to healthcare professionals for participating in non-interventional studies shall be restricted to compensation for time and expenses incurred.

6.8.5. Submission of study reports

1. Biannual progress reports on these studies shall be submitted to the Board whether it was a requirement or conducted voluntarily.

2. The Board may request progress report before the study commences or any time during the study conduct depending on the communication of risk-benefit information arising from the study or the need for information about the study progress in the context of the Board's procedures or important safety communication about the product.

3. The progress report shall include relevant information to document the progress of the study, such as the number of patients who have entered

the study, the number of exposed patients or the number of patients presenting the outcome, problems encountered and deviations from the expected plan. The progress report may include an interim report of study results.

4. An interim report submitted shall include study results of any planned interim analysis of study data before or after the end of data collection.
5. The final study report including a public abstract shall be submitted to the Board as soon as possible and not later than 12 months after the end of data collection. The content of the final study report shall be as described in (**annex 16**) of this guideline.

6.8.6. Reporting of safety and risk-benefit balance data

1. The marketing authorization holder shall monitor the data generated while the study is being conducted and consider their implications for the risk-benefit balance of the product concerned.
2. Any new information that may affect the risk-benefit balance of the product shall be communicated through pv@ppb.go.ke immediately and not later than 15 days as an emerging safety issue to the Board. The identified events shall be reported as per the reporting requirements described in section 6.1 **Submission of Individual Case Safety Reports (ICSRs)** of these guidelines.
3. Arrangements must be in place for taking appropriate urgent safety measures to protect participants against any immediate hazard where new events relating to the conduct of the study are likely to affect the safety of the participants.
4. The safety measures, such as temporarily halting the study, may be taken without prior authorization from the PPB but must be reported to the Board.
5. Information affecting the risk-benefit balance of the HPT may include an analysis of adverse reactions and aggregated data.
6. This communication is without prejudice of the information on the findings of studies which shall be provided by means of periodic safety update reports (PSURs/PBRERs) described in this guideline.

7. Individual cases of suspected adverse reactions and Serious Adverse Events that arise from the studies shall be reported to the Board in accordance to **section 6.1 on the Submission of Individual Case Safety Reports (ICSRs)**
8. Adverse events/reactions collected in studies with primary data collection shall be recorded and summarized in the interim safety analysis and in the final study report.
9. Adverse events/reactions collected in studies with secondary data collection shall be recorded and summarized in the interim safety analysis and in the final study report unless the protocol provides for different reporting with a due justification.
10. Procedures for the collection, management (including a review by the marketing authorization holder if appropriate) and reporting of suspected adverse reactions/events shall be put in place and summarized in the study protocol. If appropriate, reference can be made to the pharmacovigilance system master file but details specific to the study shall be described in the study protocol.

6.8.7. Amendments to the study protocol

1. The study protocol shall be amended and updated as needed throughout the course of the study.
2. PPB approval must be obtained for all substantial amendments that include but not limited to amendments that;
   a) Affect the safety or physical or mental integrity of the participants
   b) Affect the scientific value of the safety study,
   c) Affect the conduct or management of the study,
   d) Affect the quality or safety of drug used in the study.
   e) Change the principal investigator
   f) Change the main objective
   g) Change in-/exclusion criteria
   h) Reduce the number of monitoring visits
   i) Result in addition or reduction of sample size of the study
   j) Result in the extension of duration of the study

3. Any substantial amendments to the protocol after the study starts shall be documented in the protocol in a traceable and auditable way including the dates of the changes.
4. If changes to the protocol lead to the study being considered an interventional clinical trial, the Board shall be informed immediately and approval shall be obtained.
5. A request for approval of an amendment shall be submitted through pv@ ppb.go.ke with the following information;
   a) Summary of the proposed amendments
   b) Reason for the amendment
   c) Impact of the amendment on the original study objectives
   d) Impact of the amendments on the study endpoints and data generated.
   e) Impact of the proposed amendments on the safety and well-being of study participants.

6.8.8. Publication

1. The MAH and the investigator shall agree in advance on a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership.

2. The MAH shall be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.

3. The MAH initiating, managing or financing a non-interventional PASS shall communicate to the Board the final manuscript of the article within two weeks prior to submission for publication in order to allow the Board to review in advance the results and interpretations to be published.

4. A public abstract prior to any publishing must be approved by the Board, two (2) months prior to submitting the draft to the publisher.

7. PHARMACOVIGILANCE INSPECTIONS AND SELF-AUDITS

To ensure that MAHs and manufacturers comply with pharmacovigilance regulatory obligations and to facilitate compliance, the Board shall conduct Pharmacovigilance (PV) inspections of the companies whose products have been granted marketing authorization in Kenya.

The objectives of the PV inspections include:

i. To determine that the marketing authorization holder has personnel, systems and facilities in place to meet their pharmacovigilance obligations;
ii. To identify, record and address non-compliance, which may pose a risk to public health;
iii. To use the inspection results as a basis for regulatory/enforcement action, where considered necessary.

Any part carrying out Pharmacovigilance activities in whole or in part, on behalf of, or in conjunction with the MAH shall be inspected, in order to confirm their capability to support the marketing authorization holder's compliance with pharmacovigilance requirements.

7.1. Inspection types

Pre-authorization and post-authorization pharmacovigilance inspections shall be determined by the Board. The types of post-authorization pharmacovigilance inspections are as follows:

7.1.1. Routine inspections

Routine pharmacovigilance inspections shall be scheduled in advance as part of inspection programmes. The frequency of routine inspections may also be performed on a case-to-case basis depending on other considerations like risk analysis criteria. The MAH or manufacturer shall be notified of the planned inspection in 30 calendar days in advance. This is to ensure adequate preparation and availability of relevant individuals at the sites to be inspected. Occasionally, the Board may give a short notice when the inspection is conducted in a short time frame due to urgent safety reasons.

7.1.2. Pharmacovigilance System and product-related inspections

The Board shall conduct Pharmacovigilance system inspections. These are designed to review the procedures, systems, personnel, and facilities in place and determine their compliance with the Board pharmacovigilance requirements. As part of this review, product specific examples may be used to demonstrate the operation of the pharmacovigilance system.

Product-related pharmacovigilance inspections by the Board shall primarily focus on product-related pharmacovigilance issues, including product-specific activities and documentation, rather than a general system review. Some aspects of the general system may still be examined as part of a product-related inspection (e.g., the system used for that product).

7.1.3. Investigative or "for cause" inspections

The Board may also conduct investigative or "for cause" inspections when a trigger is recognized, and an inspection is considered an appropriate way to examine the issues. These inspections shall focus on specific pharmacovigilance processes or include an examination of identified compliance issues and their impact for a specific product. However, full system inspections may also be performed resulting from a trigger. These inspections may arise when, for example, one or more of the triggers listed below are identified:

a. Risk-benefit balance of the product:

i. Change in the risk-benefit balance where further examination through an inspection is considered appropriate;
ii. Delays or failure to identify or communicate a risk or a change in the risk-benefit balance;
iii. Communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to the Board, as applicable;
iv. Non-compliance or product safety issues identified during the monitoring of pharmacovigilance activities by the Board;
v. Suspension or product withdrawal with no advance notice to the Board

b. Reporting obligations (expedited and periodic):
   i. Delays or omissions in reporting;
   ii. Poor quality or incomplete reports;
   iii. Inconsistencies between reports and other information sources;
c. Requests from the Board
   i. Failure to provide the requested information or data within the deadline specified by the Board;
   ii. Poor quality or inadequate provision of data to fulfil requests for information from the Board:
d. Fulfilment of commitments:
   i. Concerns about the status or fulfilment of risk management plan (RMP) commitments;
   ii. Delays or failure to carry out specific obligations relating to the monitoring of product safety, identified at the time of the marketing authorization;
   iii. Poor quality of reports requested as specific obligations; inspections:
   iv. Delays in the implementation or inappropriate implementation of corrective and preventive actions;
   v. Information such as non-compliance or product safety issues from other types of inspections (GCP, GMP, GLP and GDP);
   vi. Inspection information received from other medicine regulatory authorities, which may highlight issues of non-compliance; others;
   vii. Concerns following review of the pharmacovigilance system master file;
   viii. Non-inspection related information received from other authorities, which may highlight issues of non-compliance;
   ix. other sources of information or complaints.

7.1.4. Re-inspections

Re-inspection shall take place where significant non-compliance has been identified and where it is necessary to verify actions taken to address findings and to evaluate ongoing compliance with the obligations, including evaluation of changes in the pharmacovigilance system. Re-inspection may be conducted due to the failure to implement appropriate corrective and preventive actions

in response to a previous inspection.

7.1.5. Remote inspections

These pharmacovigilance inspections shall be performed by inspectors remote from the premises of the MAH or firms employed by the marketing authorization holder. The mode of remote inspection for sites located outside Kenya shall include internet or telephone and shall involve review of documentation, safety database, source documents and pharmacovigilance system master file. Interviews of relevant staff shall be arranged where necessary. This approach may also be taken where there are logistical challenges to an on-site inspection during exceptional circumstances (e.g. a pandemic outbreak or travel restrictions). Such approaches are taken at the discretion of the Board.

In the event of non-compliance, the MAH shall be required to prepare a remedial action plan to correct the non-compliances and avoid their recurrence. The MAH shall also be required to provide reports and where necessary evidence of the progress and completion of the action plan. There may be re-inspection at an appropriate time to verify the progress and success of these remedial actions.

7.2. Frequency of conducting the pharmacovigilance inspections

Domestic or Foreign MAH or any firms employed to fulfil marketing authorization holder's pharmacovigilance obligations shall be inspected once in two (2) and three (3) years respectively depending on the type of inspection to be performed.

The Board shall plan PV inspections based on a systematic and risk-based approach to make the best use of surveillance and enforcement resources whilst maintaining a high level of public health protection.

7.3. Inspection planning

The Board shall issue a preliminary notification to the MAH about the scheduled inspection. The Board may request pertinent documents to

facilitate the inspection at least 14 days to the scheduled inspection date. The date for the inspection shall be agreed upon together with the LTR or the MAH.

7.4. Conduct of inspection

The PV inspectors from the Board, may conduct the inspections at the Local representative or the MAH's location, and if a third party is involved in any pharmacovigilance activity, their site may also be inspected by the Board. The inspection shall commence with an opening meeting and end with a closing meeting. The Local representative or the MAH has the right to choose which members of staff participates in these meetings but shall include the QPPV.

7.5. Reporting and Follow-Up

Deficiencies found during the inspections are graded as follows: **Critical**: A deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of Health Act, 2018 and applicable Pharmacy and Poisons Board guidelines.

Major: A deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of Health Act, 2018 and applicable Pharmacy and Poisons Board guidelines.

Minor: A deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

In general, preliminary findings shall be communicated at the closing meeting. An inspection report is then prepared and reviewed internally to ensure consistency of classification of deficiencies prior to issue of the final report. The report is sent to the Local representative or MAH, usually within 30 working days of the site visit or the date of the provision of the last document requested.

7.6. Sanctions

In addition, the Board may apply the following regulatory actions and sanctions:

1. The MAH or Manufacturer may be informed of non-compliance and advised on how this can be remedied.
2. Inspection to determine the extent of non-compliance and re-inspection to ensure compliance is achieved.
3. Warning: The Board may issue a formal warning reminding Local representative or Manufacturer of their pharmacovigilance regulatory obligations.
4. Product recalls especially where important safety warnings have been omitted from product information.
5. Black listing non-compliant Local representative or Manufacturer through public mechanisms.
6. The Board may consider making public a list of Local Representative or Manufacturer found to be seriously or persistently non-compliant.
7. Deferral of application for registration of product(s) until corrective and preventive actions have been implemented.
8. Urgent Safety Restriction.
9. Variation of the Marketing Authorization.
10. Suspension of the Marketing Authorization.
11. Revocation of the Marketing Authorization.
12. Fining.
13. Referral for criminal prosecution in accordance with the Kenyan legislation.

Pharmacovigilance audit activities shall serve to verify by examination and evaluation of objective evidence, the appropriateness and effectiveness of the implementation and operation of a pharmacovigilance system, including its quality system for pharmacovigilance activities.

7.7. Self-Audit

The Pharmaceutical industry shall be required to perform audits of their pharmacovigilance systems including risk-based audits of their quality

systems. Risk based audits of pharmacovigilance systems shall cover all areas listed in these guidelines. The audit shall focus on the areas of highest risk to the organization's pharmacovigilance and its quality system with the risk to public health being of prime importance.

1. Risk-based audits of the quality system shall be performed at regular intervals to ensure that the quality system complies with the quality system requirements set out in these regulations to determine its effectiveness.

2. The audit activities shall include verification, examination and evaluation of the appropriateness and effectiveness of the implementation and operation of a pharmacovigilance system and its quality system.

3. The MAH shall develop audit criteria that reflect their pharmacovigilance and quality systems and maintain records, statements or other information, which are relevant to the audit criteria and can be verified by the Board during pharmacovigilance inspections.

4. The risk-based audit shall be assessed in the following three stages;

i. Strategic level audit planning

The audit strategy is a high-level statement of how the audit activities shall be delivered over a period of time, longer than the annual programme, usually for a period of 2-5 years. The audit strategy shall include a list of audits that shall be performed including areas to be audited, methodology, assumptions, governance, risk management and internal controls of all parts of the pharmacovigilance system.

ii. Tactical level audit planning

This is a set of one or more audits planned for a specific timeframe, normally for a year. The audit programme shall be prepared in line with the long-term audit strategy and shall be risk based. The programme shall be approved by top management with overall responsibility for operational and governance

structure. The risk assessment shall focus on the quality system for pharmacovigilance activities, critical pharmacovigilance processes, key control systems and identified high risk areas in place.

iii. Operational level audit planning

Written procedures shall be in place regarding the planning and conduct of individual audits including the timeframes. The audits shall be conducted in accordance with the written procedures. The risks relevant to the area under review shall be identified and assessed during planning and shall include appropriate risk-based sampling and testing methods.

1. Audit reporting:
   i. Audit findings shall be reported in line with their relative risk level and shall be graded in order to indicate their relative criticality to risks impacting the pharmacovigilance system, processes and parts of processes. The grading system shall be defined in the description of the quality system for pharmacovigilance. The findings shall be documented in an audit report and shall be communicated to management in a timely manner and issues that need to be addressed urgently shall be reported expedited manner.
   ii. The QPPV shall be notified of any audit findings relevant to the pharmacovigilance system, irrespective of where the audit was conducted.
   iii. The marketing authorization holder shall place a note concerning critical and major audit findings of any audit relating to the pharmacovigilance system in the pharmacovigilance system master file (PSMF).

2. Actions and follow up:
   i. Corrective actions, including a follow-up audit of deficiencies, shall be taken where necessary.
   ii. The management of the organization shall be responsible for ensuring there is a mechanism in place to adequately address the issues arising from pharmacovigilance audits. Actions shall include root cause

analysis and impact analysis of identified audit findings and preparation of a corrective and preventive action plan, where appropriate.

iii. The audit shall involve evaluating the effectiveness of actions taken with the products for the purpose of minimizing risks and supporting their safe and effective use in patients.

iv. The organization shall use performance indicators to continuously monitor the good performance of pharmacovigilance activities.

v. Evaluation of audit work shall be undertaken by means of ongoing and periodic assessment of all audit activities, auditee feedback and self-assessment of audit activities (e.g. quality assurance of audit activities, compliance to code of conduct, audit programme, and audit procedures).

7.8. Auditors' qualifications, skills, experience and conduct

i. Audits shall be conducted by individuals who have no direct involvement in or responsibility for the matters or processes being audited. Pharmacovigilance audit activities shall be independent. Auditors shall be free from interference in determining the scope of auditing, performing pharmacovigilance audits and communicating audit results.

ii. Auditors shall demonstrate and maintain proficiency in terms of the knowledge, skills and abilities required to effectively conduct and/or participate in pharmacovigilance audit activities. They shall have knowledge, skills and abilities in the following:

   a. Audit principles, procedures and techniques;
   b. Applicable laws, regulations and other requirements relevant to pharmacovigilance;
   c. Pharmacovigilance activities, processes and system(s);
   d. Management system(s);
   e. Organizational system(s);
   f. Documents and information collected by the internal auditor shall be treated with appropriate confidentiality and discretion.

iii. The organization may use an outsourced audit service provider however the ultimate responsibility for the operation and effectiveness of the pharmacovigilance system resides within the organization. Documentation of the agreements shall be drawn between the organization and the service provider that shall include the scope, objectives and procedural requirements.

8. TRAINING AND CAPACITY BUILDING

The National and County governments in collaboration with PPB shall conduct capacity building for their healthcare providers.

There shall be routine training and sensitization on vigilance of HPTs and where applicable with the public health programs to the following:

- Pharmaceutical industry, MAHs.
- Healthcare Providers
- Health-related professional associations e.g., Pharmaceutical Society of Kenya (PSK), Kenya Medical Association (KMA), Kenya Pharmaceutical Association (KPA), National Nurses Association of Kenya (NNAK) etc.
- EAC Partner States in collaboration with PPB, the Regional Centre of Excellence in Pharmacovigilance.
- Patients and general public through social media, press releases and mainstream media
- Pre-service training to undergraduates and post-graduates pursuing medical related courses (medicine, pharmacy, dentistry, nursing, etc.)

Deliberate efforts shall also be channelled to train and capacity build the media on reporting of adverse reactions and events, including appropriate communication to the public.

9. SAFETY COMMUNICATION

Risk communication refers to the real-time exchange of information, advice and opinions between experts/officials and people who face a threat (hazard) to their survival, health, economic or social well-being. The goal of risk communication is to provide timely, meaningful, relevant and accurate

information, in clear and understandable terms targeted to a specific audience for minimizing the risk burden. The Board shall communicate the risk related to the quality, safety and efficacy of the health products and health technologies guided by the risk communication procedure for medicine safety.

9.1. Principles of safety communication

The following principles of safety communication shall be applied:

i. Safety communication shall deliver relevant, clear, accurate and consistent messages and reach the right audiences at the right time for them to take appropriate action;
ii. Safety communication shall be tailored to the appropriate audiences (e.g., patients and healthcare professionals) by using appropriate language and taking account of the different levels of knowledge and information needs whilst maintaining the accuracy and consistency of the information conveyed;
iii. The need for communicating safety information shall be considered throughout the pharmacovigilance and risk management process, and should be part of the risk assessment and risk minimization measures;
iv. There shall be adequate co-ordination and cooperation between the different parties involved in issuing safety communications (e.g., the Board and other relevant stakeholders);
v. Information on risks shall be presented in the context of the benefits of the health product(s) and/or technology and include available and relevant information on the seriousness, severity, frequency, risk factors, time to onset, reversibility of potential adverse reactions and expected time to recovery;
vi. Safety communication shall address the uncertainties related to a safety concern. This is of particular relevance for new information which is often communicated while the Board conducts its own evaluations; the usefulness of communication at this stage needs to be balanced against the potential for confusion if uncertainties are not properly represented;

vii. Information on competing risks such as the risk of non-treatment shall be included where appropriate;
viii. The most appropriate quantitative measures shall be used when describing and comparing risks, e.g., the use of absolute risks and not just relative risks; when comparing risks, denominators shall be the same in size. The use of other tools such as graphical presentation of the risk and/or the risk-benefit balance may also be considered;
ix. Patients and healthcare workers shall, where possible, be consulted and messages pretested early in the preparation of safety communication, particularly on complex safety concerns;
x. Where relevant safety communication shall be complemented at a later stage with follow-up communication e.g. on the resolution of a safety concern or updated recommendations;
xi. The effectiveness of safety communication shall be evaluated where appropriate and possible;
xii. Safety communications should comply with relevant requirements relating to individual data protection and confidentiality.

9.2. Target audience

The primary target audience for safety communication issued by the Board shall be patients, caregivers and healthcare workers who use (i.e. prescribe, handle, dispense, administer or take) Health products and -technologies.

The media is also a target in safety communication due to its capacity to reach out to patients, healthcare workers and the general public. Communication through the media influences public perception. It is therefore important that the media receives safety information directly from the Board in addition to any information received from other sources.

9.3. Content of safety communication

The information in the safety communication shall not be misleading and shall be presented objectively. Safety information shall not include any material or statement which might constitute advertising.

Safety communication shall contain:

i. Important new information on any authorized medical product and/or

health technology which has an impact on its respective risk-benefit balance under any conditions of use;

ii. The reason for initiating safety communication clearly explained to the target audience;
iii. Any recommendations to healthcare workers and patients on how to deal with a safety concern;
iv. When applicable, a statement on the agreement between the marketing authorization holder and the Board on the safety information provided;
v. Information on any proposed change to the product information (e.g. the summary of product characteristics (SmPC) or package leaflet (PIL));
vi. Any additional information about the use of the medical product and/or health technology and other data that may be relevant for tailoring the message to the targeted audience;
vii. A list of literature references, when relevant or a reference to where more detailed information can be found, and any other background information considered relevant;
viii. Where relevant, a reminder of the need to report suspected adverse reactions in accordance with national spontaneous reporting systems.

9.4. Communication channels

The Board shall use relevant communication tools and channels when issuing safety communication. They shall include but not limited to the following:

i. Direct Healthcare Professional Communication (DHPC);
ii. Communication materials targeted at healthcare workers;
iii. IEC materials to patients and the general public e.g. brochures, flyers, public alerts;
iv. Press communication e.g. press releases, press briefing;
v. Website;
vi. Social media and other online communications;
vii. *Inter*-NMRA communication;
viii. Responding to enquiries from the public;
ix. PvERS

x. Other means such as publications, scientific and professional journals.

9.5. Exchange of safety information produced by third parties

There are situations where new safety information is to be published or has been published (e.g., by other NMRAs, scientific journals, or any other parties). Where necessary and after evaluation, the Board shall evaluate any such safety information, and thereafter prepare and disseminate the safety announcement to address the information from the third party.

9.6. Safety communication by the marketing authorization holder

Prior to making a public safety communication, relating to information on safety concerns on the use of a Health Product and Technology, the MAH shall inform the Board of its intention to make such a communication. The MAH shall ensure that information to the public is presented objectively and is not misleading. The MAH shall disseminate the safety information only after review and approval by the Board.

Whenever an MAH becomes aware that a third party intends to issue communications that could potentially impact the risk-benefit balance of a medical product registered in Kenya, the MAH shall inform and share the content of the communications with the Board.

9.7. Publication of Direct healthcare professional communication (DHPC)

The MAH shall seek approval from the Board before dissemination of a DHPC. This communication shall be in accordance with DHPC format (**annex 17**). The Board shall also publish the final DHPC. The Board may also issue an additional safety announcement and disseminate it to relevant healthcare professionals and /or their organizations as appropriate.

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11. REVISION HISTORY

Revision no.	Date	Section(s) revised	Description of change
1	29/11/2022	2. National Pharmacovigilance section	Change of the National Safety Committee from PRAAC to Pharmacovigilance Expert Review and Advisory Committee (PERAC)
	29/11/2022	3. Roles and responsibilities 3.1 Patient/public	Addition of reporting channel USSD code *271# for public reporting
	29/11/2022	3.2 Health care provider	Addition of reporting channel mPvERS mobile application
	29/11/2022	3.4 County governments	Addition of the roles of County governments to align with the Legal notice no 96 on the Pharmacy and Poisons (Pharmacovigilance and Post market surveillance) Rules, 2022
	29/11/2022	7.3 Periodic Benefit Risk Evaluation Reports	Amendment of timelines for the submission of the PBRERs
	29/11/2022	7.5 Safety and vigilance of medical devices including in-vitro diagnostics (IVDs)	Addition of information on Reporting of adverse events and submission of investigation reports, field Safety Corrective Actions (FSCAs) and field safety notices (FSNs)
	29/11/2022	7.9.2 Post authorization efficacy studies (PAES)	Addition of a section on the conduct of PAES
2	02/01/2024	Definition of Terms	Addition of the definition of Serious Adverse Event, Mutual Recognition. Reliance and Recognition
	02/01/2024	2. The National Pharmacovigilance system	Amendment of the composition and scope of the National Pharmacovigilance System
	02/01/2024	3.1.9 Qualified Person for Pharmacovigilance	Amendment to refer the section to the Guidelines for the Establishment of Qualified Persons for Pharmacovigilance for more details
	02/01/2024	3.1.10 Pharmacovigilance Experts Review and Advisory Committee (PERAC)	Provision for co-opting specialized expertise to the committee on ad hoc basis
	02/01/2024	3.1.12 National Vaccine Safety and Advisory Committee (NVSAC)	Addition of a section on the National Safety and Advisory Committee
	02/01/2024	3.1.14 The Pharmacy and Poisons Board	This section has been moved to section 2, The National Pharmacovigilance Centre
	02/01/2024	3.2 Collaboration & Reliance in Vigilance Related Decisions	Amendment of this section to include collaboration and reliance in vigilance-related decisions.
	02/01/2024	3.3 Stakeholder Engagement	Addition of a section on stakeholder engagements in Pharmacovigilance-related activities
	02/01/2024	4 Guideline to Reporting of Adverse Events	Amendment of this section to replace “ADRs and AE” with “AEs”

Revision no.	Date	Section(s) revised	Description of change
	02/01/2024	4.2 How to recognize AEs in patients?	This section has been moved from 4.8 to 4.2
	02/01/2024	4.5 How to Report Suspected AE	Amendment of this section to include how to report all suspected adverse events
	02/01/2024	4.7 Conducting investigations on HPTs	Amendment of this section to include CHMT and National Team as part of the Investigation team. Amendment of the timelines for initiating an investigation
	02/01/2024	4.8 What happens to the reported Adverse Events	Amendment of this section to include a flow diagram
	02/01/2024	4.9 Flow of Information	Movement of this section from Section 5 to 4.9
	02/01/2024	5.1 Adverse Drug Reactions/Side Effects	Amendment of this section to Adverse Drug Reactions and Side Effects
	02/01/2024	5.4 Medication Errors	Amendment of this section to Medication Errors
	02/01/2024	5.6. Reporting poor quality health products and health technologies	Amendment of this section to include Guideline for Post-Marketing Surveillance of Medical Products and Health Technologies in Kenya
	02/01/2024	6.1 Submission of individual case safety reports (ICSRs)	Amendment of the channels for submission aggregate safety reports to the NPC
	02/01/2024	6.2 Periodic safety update reports	Amendment of the channels for submission aggregate safety reports to the NPC
	02/01/2024	6.5.1. Reporting of adverse events	Amendment of timelines for the conduct of investigations
	02/01/2024	7.5.2. Field Safety Corrective Actions (FSCAs) and Field safety Notices (FSNs)	Amendment of the template for reporting Field Safety Corrective Actions (FSCAs) and Field safety Notices (FSNs)
	02/01/2024	6.7. Case reports from published scientific literature	Amendment of the channels used for the submission of case reports
	02/01/2024	6.8 Post-Authorization Studies	Amendment of the process for application and conduct of post-authorization studies
	02/01/2024	8.1.1 Routine inspection	Amendment of timelines for notifying the manufacturer/MAH of a planned inspection
	02/01/2024	10.6 Safety communication by the marketing authorization holder	Amendment of this section to include the Review and Approval of all safety communication by the Board before dissemination.

12. LIST OF CONTRIBUTORS

The Pharmacy and Poisons Board acknowledges the immense contribution of the following for their research, compilation, and commitment to developing this guideline.

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13. ANNEXES

Annex 1: Suspected ADR reporting form

(FOM001/MIP/PMS/SOP/001)

MINISTRY OF HEALTH
PHARMACY AND POISONS BOARD
P.O. Box 27663-00506 NAIROBI
Tel: (020)-3562107 Ext 114, 0720 608811, 0733 884411 Fax: (020) 2713431/2713409
Email: pv@pharmacyboardkenya.org

IN CONFIDENCE

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

REPORT TITLE: .....

The report is on:
☐Suspected adverse drug reaction ☐Therapeutic ineffectiveness

Report Type:
☐Initial Report ☐Follow Up Report

Product category (Tick appropriate box)
☐Medicinal product ☐Blood and blood products. ☐Herbal product. ☐Cosmeceuticals. ☐Others.....

Institution details

Name of Institution	Contact/Tel No.	Facility Code:	County:

1. Patient Information
Patient name/initials: ..... IP/OP. No: .....
D.O.B/Age: ..... Patient address: ..... WARD/CLINIC:.....
(NAME/NUMBER)
Gender: ☐ Male ☐ Female

Any known allergy ☐No ☐Yes (specify).....
Pregnancy status
☐ Not Applicable ☐ Not pregnant
☐ 1st Trimester ☐ 2nd Trimester ☐ 3rd Trimester
Weight: ..... kg Height: .....cm

2. Suspected Adverse Reaction
Date of onset of reaction: .....
Brief description of reaction:.....

3. Medical History. (Other relevant history including pre-existing medical conditions e.g. allergies, smoking, alcohol use, hepatic/ renal dysfunction etc)
.....
.....

4. List all medicines being currently used by the patient including OTC, and herbal products (* Tick the suspected medicine)**

Tick (√) Suspected drug	INN/ Generic Name	Brand Name	Batch/ Lot No.	Manufacturer	Dose	Route	Frequency	Treatment Period		Indication
								Start date	Stop Date	

5. Past medication history (List all medicines used in the last 3 months including OTC, herbals, if pregnant indicate medicines used in the 1st trimester)

INN/Generic Name	Brand Name	Batch/Lot No.	Manufacturer	Dose	Route	Frequency	Treatment Period		Indication
							Start date	Stop date	

6. Dechallenge/Rechallenge
Did the reaction resolve after the drug was stopped or when the dose was reduced?
☐ Yes. ☐No ☐Unknown. ☐N/A
Did the reaction reappear after the drug was reintroduced?
☐ Yes. ☐ No. ☐Unknown ☐ N/A

7. Any lab investigations and results.....
.....

8. Grading of the reaction /event
I. Severity of reaction : ☐ Mild ☐ Moderate ☐ Severe ☐ Fatal ☐ Unknown
II. Is the reaction serious? ☐Yes ☐No
III. Criteria/reason for seriousness : ☐ Hospitalization/Prolonged Hospitalization ☐ Disability. ☐ Congenital anomality ☐ Life threatening ☐ Death
IV. Action taken : ☐ Drug withdrawn. ☐ Dose reduced. ☐ Dose increased. ☐ Dose not changed ☐ Not applicable. ☐ Unknown
V. Outcome : ☐ Recovered. ☐ Recovered with sequelae. ☐ Recovering ☐ Not recovered ☐ Death. ☐ Unknown

9. Any other comment .....
.....

10. Reporter Details

Name of Initial reporter:	Cadre/designation:	Mobile no: Email:	Date of report:
Name of Person Submitting to PPB if different from reporter:	Cadre/designation:	Mobile no: Email:	Date of Submission:

You need not be certain..... just be suspicious!

Your support towards the National Pharmacovigilance system is appreciated
Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the event.
Patient's identity is held in strict confidence and program staff is not is not expected to and will not disclose reporter's identity in response to any public request.
Information supplied by you will contribute to the improvement of drug safety and therapy in Kenya. Once completed please send to:
The Pharmacy and Poisons Board on the above address

FOR OFFICIAL (PPB) USE ONLY	
ADR Report No: ...../...../.....	Date Received ...../...../.....
Vigiflow Entry Number.....	Date Committed ...../...../.....

Annex 2: AEFI Reporting Form

MINISTRY OF HEALTH

UNIT OF VACCINES AND IMMUNIZATION SERVICES

AEFI Reporting Form

(To be filled in triplicate) ☐ Initial Report ☐ Follow-up report

NAME OF REPORTING INSTITUTION.....INSTITUTION MFL CODE.....

COUNTY..... SUB-COUNTY.....

Patient Details

PATIENT'S NAME..... IP/OP NO..... DATE OF BIRTH(or age in months).....

GENDER..... NAME OF GUARDIAN (If patient is a child).....

ADDRESS..... PHONE NUMBER(self or nearest contact).....

VILLAGE..... WARD..... SUB-COUNTY..... COUNTY.....

VACCINATION CENTRE..... COUNTY OF VACCINATION CENTRE.....

TYPE OF VACCINATION SERVICE (static, mass, outreach).....

Type of AEFI Please tick:		Brief details on the event (including timeline of occurrence)
BCG Lymphadenitis ☐	Anaphylaxis ☐	.....
Convulsion ☐	Encephalopathy, Encephalitis/Meningitis ☐	.....
Generalized urticaria (hives) ☐		.....
High Fever ☐	Paralysis ☐	.....
Injection site abscess ☐	Toxic shock ☐	.....
Severe Local Reaction ☐	Others (specify)..... ☐	.....

Onset of event: Date ..... /..... /..... Time .....

Suspected vaccine(s)

Name of Vaccine(e.g. BCG, DPT-Hib-HeB)	Dose No.	Date vaccinated	Route,site of vaccination (i.m.,s.c., i.d.)	Details of Vaccine			Details of Diluents		
				Lot/Batch No.	Manufacturer's Name	Expiry Date	Lot/Batch No.	Manufacturer's Name	Expiry Date

Past medical history (including history of similar reaction or other allergies, concomitant medication/vaccine,concomitant illness, other cases,pregnacy status and other relevant information*(continue on separate sheet if necessary)*

.....

.....

.....

Action taken ☐ Treatment given (specify).....

☐ Specimen collected for investigation (specify type(s) of specimen).....

AEFI Outcome ☐ Recovered ☐ Recovering ☐ Not recovered ☐ Unknown ☐ Died

Name of Person Reporting.....Phone No..... Email.....

Designation..... Signature: ..... Date: .....

Final Classification of AEFI (*to be filled at national level*):

(See overleaf for guidelines on how to complete the form)

Annex 3: Adverse transfusion reaction form

(FOM20/MIP/PMS/SOP/001

MINISTRY OF HEALTH
PHARMACY AND POISONS BOARD
P.O. Box 27663-00506NAIROBI
Tel: (020)-3562107 Ext 114, 0720 608811, 0733 884411 Fax: (020) 2713431/2713409
Email: pv@pharmacyboardkenya.org

IN CONFIDENCE

ADVERSE TRANSFUSION REACTION FORM

In the event of a severe reaction following transfusion of blood or blood products please complete this form and send it to the laboratory with the specimens listed below.

PATIENT INFORMATION

Patient name:_____ Age: _____
Gender: ☐ Male ☐ Female Patient No.: _____

Diagnosis: _____
Ward:_____
Pre-transfusion HB: _____
Reason for transfusion: _____
Current Medications: _____

Obstetric History: ☐ N/A ☐ Gravid_____☐ Para ____
Previous Transfusion: ☐ Yes ☐ No
Comment: _____
Previous Reactions: ☐ Yes ☐ No
Comment: _____

REACTION INFORMATION

Type of reaction
1. General: ☐ Fever ☐ Chills/Rigors ☐ Flushing
☐ Nausea/ Vomiting
2. Dermatological: ☐ Urticaria, ☐ Other skin rash
3. Cardiac/Respiratory: ☐ Chest pain ☐ Dyspnoea
☐ Hypotension ☐ Tachycardia
4. Renal: ☐ Haemoglobinuria- Dark urine ☐ Oliguria
☐ Anuria
5. Haematological: ☐ Unexplained bleeding
6. Others (Specify): _____

Vital Signs: At Start: BP_____ During (15min) BP _____ At stop: BP_____
T_____ T _____ T_____
P_____ P _____ P_____
R_____ R _____ R _____

COMPONENT INFORMATION

Name of Nurse/Doctor: _____

Signature: _____

Type of component	Pint No	Expiry Date	Volume Transfused

Specimens required by the laboratory

1. *10mls post-transfusion whole blood from patient from plain bottle*
2. *2mls of blood in EDTA bottle*
3. *10mls First Void Urine*
4. *The blood that reacted together with the attached transfusion set*
5. *All empty blood bags of already transfused unit*

LAB INVESTIGATION: (Transfusion manager)

1. Recipient's blood supernatant:
Hemolysis ☐Present ☐ Absent ☐ Equivocal
If present ☐ Mild ☐ Moderate ☐ Marked
2. Recipient's blood:
Agglutination ☐ Present ☐ Absent
3. Haematological results: WBC_____HB_____RBC_____HCT_____MCV _____
MCH_____MCHC_____PLT _____

Film Rbc:_____Wbc:_____Plt: _____

4. Donor blood supernatant:
Hemolysis ☐ Present ☐ Absent

5. Age of donor pack: _____

6. Culture donor pack: Results: _____

7. Culture recipient blood: Results: _____

8. Compatibility testing recipient serum (pretransfusion sample) and donor cells (pack)

Compatible	Saline Rt	☐	Saline 37	☐	AHG	☐	Albumin 37 ☐
Incompatible	Saline Rt	☐	Saline 37	☐	AHG	☐	Albumin 37 ☐

9. If negative (inconclusive results in 8) set up compatibility with enzyme treated cells Result: _____

10. In case of blood group O transfused to A or B or AB individual: Establish from the donor unit
Anti A titres_____Anti B titers _____

11. Urinalysis _____
12. Evaluation: Diagnosis
13. Was the adverse reaction related to transfusion?
☐ Yes ☐ No ☐ Inconclusive

Reporter Details

Name of Initial reporter:	**Cadre/designation:**	**Mobile no:** **Email:**	**Date of report:**
Name of Person Submitting to PPB if different from reporter:	**Cadre/designation:**	**Mobile no:** **Email:**	**Date of Submission:**

You need not be certain..... just be suspicious!

Your support towards the National Pharmacovigilance system is appreciated
Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the event.
Patient's identity is held in strict confidence and program staff is not is not expected to and will not disclose reporter's identity in response to any public request.
Information supplied by you will contribute to the improvement of drug safety and therapy in Kenya. Once completed please send to:
The Pharmacy and Poisons Board on the above address

FOR OFFICIAL (PPB USE ONLY)	
ADR Report No: ...../...../.....	Date Received.....
Vigiflow Entry Number	Date Committed: .....

Annex 4: Medical devices incident reporting form

(FOM019/MIP/PMS/SOP/001)

MINISTRY OF HEALTH
PHARMACY AND POISONS BOARD
P.O. Box 27663-00506 NAIROBI
Tel: (020)-3562107 Ext 114, 0720 608811, 0733 884411 Fax: (020) 2713431/2713409
Email: pv@pharmacyboardkenya.org/medicaldevices@pharmacyboardkenya.org

IN CONFIDENCE

MEDICAL DEVICES INCIDENT REPORTING FORM

Report Type: ☐ **Initial Report** ☐ **Follow Up Report**

REPORT TITLE: .....

NAME OF INSTITUTION/ORGANZIATION: .....INSTITUTION CODE: .....

ADDRESS: ..... CONTACT: .....

Patient Information

Patient name/initials..... D.O.B/age..... Patient address: ..... IP/OP No: ..... Gender: ☐ Male ☐ Female

Any known allergy
☐ No
☐ Yes (specify)

Pregnancy status
☐ Not Applicable
☐ Not pregnant ☐ 1st Trimester ☐ 2nd Trimester ☐ 3rd Trimester

Weight: ..... kg
Height: .....cm

Device/In vitro Diagnostic information

1. Problem noted prior to use: ☐ Yes ☐ No

Brand name/commercial name:	Serial/Lot no:	
Common name (catheter; syringe 5cc,10cc; latex gloves etc.):	Model:	Catalogue:
Name of manufacturer:	Address of the manufacturer:	
Device manufacture date:	Expiry date:	

2. Operator of the device at time of onset:
☐ Healthcare professional ☐ Patient ☐ Caregiver ☐ Other(specify).....
3. Usage of device (choose whichever applies): ☐ Single use ☐ Reuse of reusable ☐ Reuse of single-use ☐ Reserviced/Refurbished
4. How long was the device/ equipment/ machine in use: .....
5. Availability of device for evaluation ☐ Yes ☐ No
6. If no: ☐ Device destroyed ☐ Still in use ☐ Returned to manufacturer/importer/distributor

7. For implants only (e.g. intrauterine devices, pacemakers)

Implant date:	Explant date:
Duration of implantation (to be filled if the exact implant and explant dates are unknown):	

8. For diagnostics only (including machines and equipment e.g. rapid diagnostic test kits, glucometer)

Type of specimen used (e.g. blood, saliva, etc):		
No. of patients involved:	No. of tests done:	No. of false positives:
No. of false negatives:	No. of true positives:	No. of true negatives:

9. List of other/associated devices involved in the event:

Incident information

1. Date of onset of the incident:
2. Event classification ☐Fatal ☐ Serious ☐ Moderate ☐ Mild ☐ Unknown
3. Reason for seriousness:
☐ Death (dd/mm/yyyy) .... /...../..... ☐ Life-threatening
☐ Hospitalization or prolongation of existing hospitalization
☐ Results in persistent or significant disability
☐ congenital anomaly or birth defect ☐ Congenital anomaly or birth defect
4. Description of event .....

5. Remedial Action/Corrective action/preventive action taken by the healthcare facility relevant to the care of the patient:
.....
.....

6. Patient Outcome:

☐ Recovering ☐ Not recovered ☐ Fatal
☐ Recovered ☐Recovered with sequalae ☐ Unknown

Details of the reporter:

Name of reporter:	Designation:	Email: Mobile no:	Date:
Name of Person Submitting if Different from Reporter	Designation:	Email: Mobile no:	Date of submission:

You need not be certain..... just be suspicious!

Your support towards the National Pharmacovigilance system is appreciated

The Pharmacy and Poisons Board investigates all incidents reported to us in order to identify any faults with medical devices and to prevent similar incidents happening again. The Board may contact the manufacturer of this medical device to request they carry out an investigation. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the event. Patient's identity is held in strict confidence. Information supplied by you will contribute to the improvement of the safety of medical devices in Kenya.

FOR OFFICIAL (PPB) USE ONLY
Incident Report No: ...../...../..... Date Received ...../...../.....
Vigiflow Entry Number..... Date Committed ...../...../.....

Annex 5: Medication errors reporting form

(FOM21/MIP/PMS/SOP/001)

MINISTRY OF HEALTH
PHARMACY AND POISONS BOARD
P.O. Box 27663-00506 NAIROBI
Tel: (020)-3562107 Ext 114, 0720 608811, 0733 884411 Fax: (020) 2713431/2713409
Email: pv@pharmacyboardkenya.org

IN CONFIDENCE

MEDICATION ERROR REPORTING FORM

1. Date of event (dd/mm/yyyy):...../...../..... **2. Time of event** (hh/mm): .....

3. Institution details

Name of Institution:	Contact/Tel No:	Facility Code:	County:

4. Patient Information

Patient initials: ..... D.O.B/Age: ..... Gender: ☐ Male ☐ Female

5. Details on the medication error

Location of event:

☐ Ward (Specify: medical, paeds, ortho) .....
☐ Clinic (Specify: outpatient, dental, specialist) .....
☐ Pharmacy (paeds, main, inpatient, outpatient) .....
☐ Accident & Emergency/Casualty
☐ Others: (Please specify) .....

6. Please describe the error. Include description/ sequence of events and work environment (e.g. change of shift, short staffing, during peak hours). If more space is needed, please attach a separate page. .....

7. In which process did the error occur?
☐ Prescribing
☐ Dispensing (includes filling)
☐ Administration
☐ Others (Please specify)
.....

8. Did the error reach the patient?
☐ Yes ☐ No

9. Was the correct medication, dose or dosage form administered to or taken by the patient?
☐ Yes ☐ No

10. Describe the direct result on the patient (e.g. death, type of harm, additional patient monitoring e.g. BP, heart rate, glucose level etc)
.....
.....
.....

11. Please tick the appropriate Error Outcome Category (Tick one appropriate box below):

NO ERROR	ERROR, HARM	
☐ Potential error, circumstances/events have potential to cause incident	☐ Treatment /intervention required-caused temporary harm ☐ Initial/prolonged hospitalization-caused temporary harm	☐ Caused permanent harm ☐ Near death event

ERROR, NO HARM		ERROR, DEATH
☐Actual error-did not reach patient	☐ Actual error-caused no harm ☐ Additional monitoring required-caused no harm	☐ Death

12. Indicate the possible error cause(s) and contributing factor(s) below (Tick the appropriate box(es):

Staff factors	Work and environment	Task and technology
☐ Inexperienced personnel	☐Heavy workload	☐ Failure to adhere to work procedure
☐ Inadequate knowledge	☐ Peak hour	☐ Use of abbreviations
☐ Distraction	☐ Stock arrangements/storage problem	☐ Illegible prescriptions
Medication related		☐ Patient information/record unavailable/ inaccurate
☐ Sound alike medication		☐ Wrong labelling/instruction on dispensing envelope or bottle/container
☐ Look alike medication		☐ Incorrect computer entry
☐ Look alike packaging		☐ Others (please specify): .....

13. Product details: Please complete the following for products involved. Kindly attach a separate page for additional products

Product Description	Product No. 1 (intended)	Product No. 2 (error)
13.1 Generic name (active ingredient)		
13.2 Brand/ Product Name		
13.3 Dosage form		
13.4 Dose, frequency, duration, route		

Please fill in 13.5-13.7 if error involved look alike (similar) product packaging:

Product Description	Product No. 1 (intended)	Product No. 2 (error)
13.5 Manufacturer		
13.6 Strength/concentration		
13.7 Type and size of container		

14. Suggest any recommendations, or describe policies or procedures you instituted or plan to institute to prevent future similar errors. If available, kindly attach an investigational report e.g. Root Cause Analysis (RCA) .....
.....

Reporter Details

Name of Initial reporter:	Cadre/designation:	Mobile no: Email:	Date of report:
Name of Person Submitting to PPB if different from reporter	Cadre/designation:	Mobile no: Email:	Date of Submission:

FOR OFFICIAL (PPB) USE ONLY	
Medication error report no: ...../...../.....	Medication error type.....
Date report received (dd/mm/yyyy):...../...../.....	Medication error category .....
Vigiflow Entry Number..... Date Committed ...../...../.....	

Your support towards the National Pharmacovigilance system is appreciated

Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the event.

Patient's identity is held in strict confidence and program staff is not is not expected to and will not disclose reporter's identity in response to any public request. Information supplied by you will contribute to the improvement of medicine safety and therapy in Kenya.

Once completed please send to: The Pharmacy and Poisons Board on the above address

Annex 6: Form for reporting suspected poor-quality HPTs

(FOM001/MIP/PMS/SOP/001)

MINISTRY OF HEALTH
PHARMACY AND POISONS BOARD
P.O. Box 27663-00506 NAIROBI
Tel: (020)-3562107 Ext 114, 0720 608811, 0733 884411 Fax: (020) 2713431/2713409
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IN CONFIDENCE

FORM FOR REPORTING SUSPECTED POOR-QUALITY MEDICAL PRODUCTS AND HEALTH TECHNOLOGIES

Product category (Tick appropriate box):

☐Medicinal product ☐Blood and blood products. ☐Other.....
☐Herbal product ☐Medical device
☐Vaccine ☐Cosmeceuticals

Name of Facility: County: Sub- County:
Facility Address. Facility Telephone:

PRODUCT IDENTITY

Brand Name				Generic Name			
Batch/Lot Number/ Unique identifiers (blood & blood products)		Date of Manufacture		Date of Expiry		Date of Receipt	
Name of Manufacturer		Address		Country of Origin			
Name of Distributor/ Supplier		Distributor/ Supplier's Address			Telephone		

PRODUCT FORMULATION (Tick appropriate box)

☐Oral tablets/capsules ☐Powder for reconstitution of injection
☐Oral suspension/syrup ☐Eye drops
☐Injection ☐Ear drops
☐Diluent ☐Nebuliser solution
☐Powder for reconstitution of suspension
☐Cream / Ointment / Liniment / Paste
☐Other .....

COMPLAINT (Tick appropriate box/boxes)

☐Color change ☐Moulding
☐Separating ☐Change of Oduor
☐Powdering / crumbling ☐Mislabeling
☐Caking ☐Incomplete pack
☐Therapeutic ineffectiveness
☐Other.....

Describe complaint in detail.....
.....
Was the cold chain maintained for both transportation and storage?.....
.....(Attach sample for physical evaluation)

Storage Conditions

Does the product require refrigeration?	☐ Yes	☐ No	Other details (if necessary):
Was product available at facility?	☐ Yes	☐ No	
Was product dispensed and returned by client?	☐ Yes	☐ No	
Was product stored according to manufacturer / MoH recommendations?	☐ Yes	☐ No	

Comments (if any):

Name of Reporter:	Contact Number:	E-mail:
Cadre/Designation:	Signature	Date:

FOR OFFICIAL (PPB) USE ONLY

Report No: ...../...../.....

Your support towards the National Pharmacovigilance system is appreciated
Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the event.
Patient's identity is held in strict confidence and program staff is not is not expected to and will not disclose reporter's identity in response to any public request.
Information supplied by you will contribute to the improvement of drug safety and therapy in Kenya. Once completed please send to:
The Pharmacy and Poisons Board on the above address

Annex 7: ADR severity assessment scale

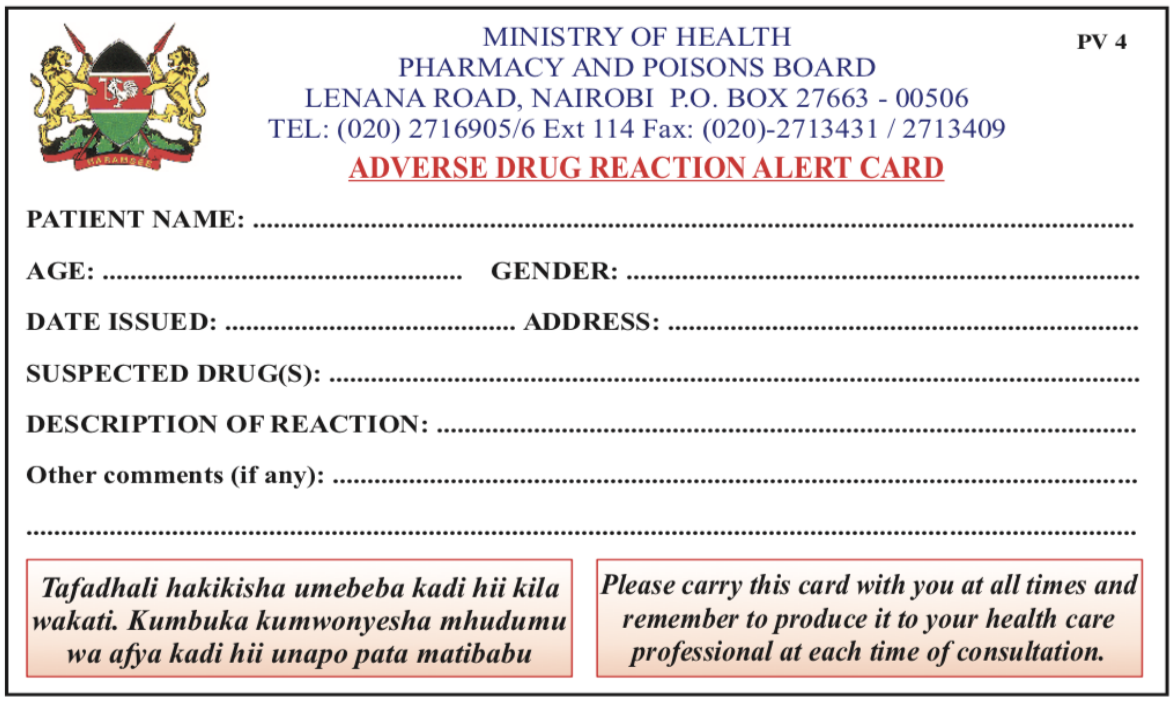
Criteria for Assessment of Severity of an ADR

Mild	● The ADR requires no change in treatment with the suspected drug ● The ADR requires that the suspected drug be withheld, discontinued or otherwise changed. No antidote or other treatment is required ● No increase in length of stay.
Moderate	● The ADR requires that the suspected drug be withheld, discontinued or otherwise changed, and/or an antidote or other treatment is required. ● Increases length of stay by at least one day ● The ADR is the reason for admission.
Severe	● The ADR requires intensive medical care ● The ADR causes permanent harm to the patient
Fatal	● The ADR either directly or indirectly leads to the death of the patient
Unknown	● When you have no information about the ADR

Annex 8: WHO-UMC Causality assessment scale

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional / Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable / Unclassified	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Annex 9: Adverse drug reaction alert card



MINISTRY OF HEALTH
PHARMACY AND POISONS BOARD
LENANA ROAD, NAIROBI P.O. BOX 27663 - 00506
TEL: (020) 2716905/6 Ext 114 Fax: (020)-2713431 / 2713409

PV 4

ADVERSE DRUG REACTION ALERT CARD

PATIENT NAME: .....

AGE: ..... **GENDER:** .....

DATE ISSUED: ..... **ADDRESS:** .....

SUSPECTED DRUG(S): .....

DESCRIPTION OF REACTION: .....

Other comments (if any): .....

.....

Tafadhali hakikisha umebeba kadi hii kila wakati. Kumbuka kumwonyesha mhudumu wa afya kadi hii unapo pata matibabu

Please carry this card with you at all times and remember to produce it to your health care professional at each time of consultation.

Criteria for issue of a patient alert card (rear side)

The alert card is given to:

- Patients who are hypersensitive / allergic / intolerant to a particular drug
- Patients who developed a 'near-fatal' reaction to any particular drug
- Patients who had a drug-induced morbidity to any drug
- Patients who had hospital admission due to an ADR to any drug
- Patients who developed an ADR which caused increase in the health care expenditure

Annex 10: Checklist for investigation procedure for serious ADRs by the Sub-County Investigation Team (SCIT)

CHECKLIST FOR INVESTIGATION PROCEDURE FOR THE SCIT	
Step	**Actions**
1) Confirm information in Report	☐ Obtain patient's medical file (or other clinical record) ☐ Check details about patient and event from medical file and document information ☐ Obtain any details missing from suspected ADR notification form ☐ Identify any other cases that need to be included in the
2) Investigate and collect data: About the patient:	☐ History of drug use (including over-the-counter and traditional medicine use) ☐ Medical history, including prior history of similar reactions or allergies ☐ Family history of similar events
About the event:	☐ History, clinical description, any relevant laboratory results about the suspected ADR and diagnosis of the event ☐ Treatment, whether hospitalized, and outcome
About the suspected drug(s):	☐ Brand name, generic name, batch/lot numbers ☐ Date of manufacture, date of expiry ☐ Name of manufacturer and supplier ☐ Conditions of storage at facility and expiry date ☐ Investigate the local health facility
About other people:	☐ Whether others received the same drug and developed illness (assess health facility ledgers) ☐ Whether others had same or similar illness (may need case definition); if so exposure of cases to suspect drug(s)
3) Assess the service by asking about	☐ Drug storage and prescription ☐ Details of training in diagnosis and treatment ☐ Number of therapies greater than normal
4) Formulate a working Hypothesis	☐ On the likely/possible cause(s) of the event
5) Test working hypothesis	☐ Does case distribution match working hypothesis? ☐ Occasionally, laboratory tests may help
6) Conclude investigation	☐ Assess causal association to suspected drug/s ☐ Complete suspected ADR Investigation Form ☐ Take corrective action, and recommend further action
7) Assess outcome of actions/ lack of actions taken	☐ Assess impact of any corrective action taken (where appropriate)

Annex 11: AEFI investigation form

AEFI INVESTIGATION FORM

(Only for Serious Adverse Events Following Immunization – Death / Disability / Hospitalization / Cluster)

Section A **Basic details**

Province/State **District** **Case ID**

Place of vaccination (✓): ☐ Govt. health facility ☐ Private health facility ☐Other (specify) _____
Vaccination in (✓): ☐ Campaign ☐ Routine ☐ Other (specify) _____

Address of vaccination site:

Name of Reporting Officer:

Date of investigation: __ __ / __ __ / __ __ __ __
Date of filling this form: __ __ / __ __ / __ __ __ __

Designation / Position:

This report is: ☐ *First* ☐ *Interim* ☐ *Final*

Telephone # landline (with code): Mobile: e-mail:

Patient Name Sex: ☐M ☐ F

(use a separate form for each case in a cluster)

Date of birth (DD/MM/YYYY): __ __ / __ __ / __ __ __ __

OR Age at onset: __ __ *years* __ __ *months* __ __ __ *days* *OR Age group:* ☐ *< 1 year* ☐ *1–5 years* ☐ *> 5 years*

Patient's full address with landmarks *(Street name, house number, locality, phone number etc.)*:

Name of vaccines/diluent received by patient	Date of vaccination	Time of vaccination	Dose (e.g. 1st, 2nd, etc.)	Batch/Lot number	Expiry date
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent

Type of site (✓) ☐ Fixed ☐ Mobile ☐ Outreach ☐ Other _____

Date of first/key symptom *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __ Time of first symptom *(hh/mm)*: __ __ / __ __
Date of hospitalization *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __
Date first reported to the health authority *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __

Status on the date of investigation (✓): ☐ Died ☐ Disabled ☐ Recovering ☐ Recovered completely ☐Unknown

If died, date and time of death *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __ *(hh/mm)*: __ __ / __ __
Autopsy done? (✓) ☐ Yes (date)_____ ☐ No ☐ Planned on (date)_____ Time_____
Attach report (if available)

Section B **Relevant patient information prior to immunization**

Criteria	Finding	Remarks (If yes provide details)
Past history of similar event	Yes / No / Unkn	
Adverse event after previous vaccination(s)	Yes / No / Unkn	
History of allergy to vaccine, drug or food	Yes / No / Unkn	
Pre-existing illness (30 days) / congenital disorder	Yes / No / Unkn	
History of hospitalization in last 30 days, with cause	Yes / No / Unkn	
Patient currently on concomitant medication? (If yes, name the drug, indication, doses & treatment dates)	Yes / No / Unkn	
Family history of any disease (relevant to AEFI) or allergy	Yes / No / Unkn	

For adult women
- Currently pregnant? Yes (weeks) _____ / No / Unknown
- Currently breastfeeding? Yes / No

For infants
The birth was ☐ full-term ☐ pre-term ☐ post-term. Birth weight:

Delivery procedure was ☐ Normal ☐ Caesarean ☐ Assisted (forceps, vacuum etc.) ☐ with complication (specify)

Section C	**Details of first examination** of serious AEFI case**	
Source of information (✓ *all that apply*): ☐ **Examination by the investigator** ☐ **Documents** ☐ **Verbal autopsy** ☐ **Other**_____ *If from verbal autopsy, please mention source* _____		
Name of the person who first examined/treated the patient:_____ Name of other persons treating the patient: _____ Other sources who provided information (specify): _____		
Signs and symptoms in chronological order from the time of vaccination:		
Name and contact information of person completing these clinical details:	Designation:	Date/time

****Instructions – Attach copies of ALL available documents (including case sheet, discharge summary, case notes, laboratory reports and autopsy reports) and then complete additional information NOT AVAILABLE in existing documents, i.e.**

- ***If patient has received medical care*** – attach copies of all available documents (including case sheet, discharge summary, laboratory reports and autopsy reports, if available) and write only the information that is not available in the attached documents below
- ***If patient has not received medical care*** – obtain history, examine the patient and write down your findings below (add additional sheets if necessary)

Provisional / Final diagnosis:

Section D	Details of vaccines provided at the site linked to AEFI on the corresponding day									
Number immunized for each antigen at session site. Attach record if available.	Vaccine name									
	Number of doses									

a) When was the patient immunized? (✓ the ☐ below and respond to ALL questions)	
☐ Within the first vaccinations of the session ☐ Within the last vaccinations of the session ☐ Unknown	
In case of multidose vials, was the vaccine given ☐ within the first few doses of the vial administered? ☐ within the last doses of the vial administered? ☐ unknown?	
b) Was there an error in prescribing or non-adherence to recommendations for use of this vaccine?	Yes* / No
c) Based on your investigation, do you feel that the vaccine (ingredients) administered could have been unsterile?	Yes* / No / Unable to assess
d) Based on your investigation, do you feel that the vaccine's physical condition (e.g. colour, turbidity, foreign substances etc.) was abnormal at the time of administration?	Yes* / No / Unable to assess
e) Based on your investigation, do you feel that there was an error in vaccine reconstitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	Yes* / No / Unable to assess
f) Based on your investigation, do you feel that there was an error in vaccine handling (e.g. break in cold chain during transport, storage and/or immunization session etc.)?	Yes* / No / Unable to assess
g) Based on your investigation, do you feel that the vaccine was administered incorrectly (e.g. wrong dose, site or route of administration, wrong needle size, not following good injection practice etc.)?	Yes* / No / Unable to assess
h) Number immunized from the concerned vaccine vial/ampoule	
i) Number immunized with the concerned vaccine in the same session	
j) Number immunized with the concerned vaccine having the same batch number in other locations. Specify locations: _____	
k) Is this case a part of a cluster?	Yes* / No / Unkn
i. If yes, how many other cases have been detected in the cluster?	
a. Did all the cases in the cluster receive vaccine from the same vial?	Yes* / No / Unkn
b. If no, number of vials used in the cluster (enter details separately)	

It is compulsory for you to provide explanations for these answers separately

Section E Immunization practices at the place(s) where concerned vaccine was used

(Complete this section by asking and/or observing practice)

Syringes and needles used:

• Are AD syringes used for immunization?	Yes / No / Unkn

If no, specify the type of syringes used: ☐ Glass ☐ Disposable ☐ Recycled disposable ☐ Other _____

Specific key findings/additional observations and comments:

Reconstitution: (complete only if applicable, ✓ NA if not applicable)

	Status		
• Reconstitution procedure (✓)			
Same reconstitution syringe used for multiple vials of same vaccine?	Yes	No	NA
Same reconstitution syringe used for reconstituting different vaccines?	Yes	No	NA
Separate reconstitution syringe for each vaccine vial?	Yes	No	NA
Separate reconstitution syringe for each vaccination?	Yes	No	NA
• Are the vaccines and diluents used the same as those recommended by the manufacturer?	Yes	No	NA

Specific key findings/additional observations and comments:

Section F	Cold chain and transport *(Complete this section by asking and/or observing practice)*
Last vaccine storage point:	
• Is the temperature of the vaccine storage refrigerator monitored?	Yes / No
○ If "yes", was there any deviation outside of 2–8° C after the vaccine was placed inside?	Yes / No
○ If "yes", provide details of monitoring separately.	
• Was the correct procedure for storing vaccines, diluents and syringes followed?	Yes / No / Unkn
• Was any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes / No / Unkn
• Were any partially used reconstituted vaccines in the refrigerator?	Yes / No / Unkn
• Were any unusable vaccines (expired, no label, VVM at stages 3 or 4, frozen) in the refrigerator?	Yes / No / Unkn
• Were any unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?	Yes / No / Unkn
Specific key findings/additional observations and comments:	
Vaccine transportation:	
• Type of vaccine carrier used	
• Was the vaccine carrier sent to the site on the same day as vaccination?	Yes / No / Unkn
• Was the vaccine carrier returned from the site on the same day as vaccination?	Yes / No / Unkn
• Was a conditioned ice-pack used?	Yes / No / Unkn
Specific key findings/additional observations and comments:	

Section G Community investigation (Please visit locality and interview parents/others)

Were any similar events reported within a time period similar to when the adverse event occurred and in the same locality?
Yes / No / Unknown If yes, describe:

If yes, how many events/episodes?

Of those effected, how many are
- Vaccinated:_____
- Not vaccinated:_____
- Unknown:_____

Other comments:

Section H Other findings/observations/comments

Annex 12: Examples of AEFIs

Reportable AEFI	Onset time interval if vaccine/vaccination is implicated
•Anaphylactoid reaction (acute hypersensitivity reaction) •Anaphylaxis •Persistent inconsolable screaming (more than 3 hours) •Hypotonic hypo-responsive episode (HHE) •Toxic shock syndrome (TSS)	Within 24 to 48 hours of immunization
•Severe local reaction •Sepsis •Injection site abscess (bacterial/sterile)	Within 7 days of immunization
•Seizures, including febrile seizures (6-12 days for measles/MMR; 0-2 days for DTP) •Encephalopathy (6-12 days for measles/MMR; 0-2 days for DTP)	Within 14 days of immunization
•Acute flaccid paralysis (4-30 days for OPV recipient; 4-75 days for contact) •Brachial neuritis (2-28 days after tetanus containing vaccine) •Intussusception (commonly within 21 days after rotavirus vaccines) •Thrombocytopenia (15-35 days after measles/MMR)	Within 3 months of immunization
•Lymphadenitis • Disseminated BCG infection • Osteitis /Osteomyelitis	Between 1 and 12 months after BCG immunization
•Death •Hospitalization •Disability •Any other severe and unusual events that are thought by healthcare professionals or the public to be related to immunization	No time limit

Annex 13: RMP Outline and format

Part I Product(s) overview
Part II Safety specification
Section SI Epidemiology of the indication(s) and target population(s)
Section SII Non-clinical part of the safety specification
Section SIII Clinical trial exposure
Section SIV Populations not studied in clinical trials
Section SV Post-authorization experience
Section SVI Additional PPB requirements for the safety specification
Section SVII Identified and potential risks
Section SVIII Summary of the safety concerns
Part III Pharmacovigilance plan (including post-authorization safety studies)
Part IV Plans for post-authorization efficacy studies
Part V Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)
Part VI Summary of the risk management plan
Part VII Annexes

1. Product Overview

Details to be captured include active substance, pharmacotherapeutic group, name of the marketing authorization applicant for initial marketing authorization applications, marketing authorization holder for RMPs submitted with post-authorization procedures, medicinal product(s) to which this RMP refers. Authorization procedure(s) (centralised, mutual recognition, decentralised, national); brief description of the product including: chemical class; summary of mode of action; composition (e.g. origin of active substance of biologicals, relevant adjuvants or residues for vaccines); indications and pharmaceutical form and strengths.

2. Safety Specifications

This section should provide adequate information on the safety profile of medicinal product with focus on aspects that need further risk management activities. This section should contain a description of each of the eight modules as listed below:

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

ix. Pharmacovigilance plan (including post-authorization safety studies)

Refer to the current version of ICH PV planning E2E

3. Summary of the Risk Management Plan

This section should provide a risk minimization plan for each of the safety concerns raised in the safety specification sections. It should include both routine and any other risk minimizations including justification and indicators to measure the effectiveness of the plan.

4. RMP Annexes

i. Tabulated summary of planned, on-going, and completed pharmacovigilance study programme.
ii. Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan
iii. Specific adverse event follow-up forms
iv. Protocols for proposed and on-going studies in RMP part IV
v. Details of proposed additional risk minimization activities
vi. Other supporting data (including referenced material)
vii. Summary of changes to the risk management plan over time

5. QPPV Declaration for Risk Management Plan

1. I, the undersigned certify that all the information in Risk Management Plan and accompanying documentation is correct, complete and true to the best of my knowledge.
2. I further confirm that the information on all Risk Management activities will be available for verification during Good Pharmacovigilance Practice (GVP) inspection.
3. I also agree that, I the Qualified Person for Pharmacovigilance in collaboration with the Marketing Authorization Holder (MAH) will implement all activities contained in the Risk Management and Pharmacovigilance plans for this product in accordance with the Board requirements.
4. I also agree that I am obliged to follow all the requirements by the Board in ensuring the quality, safety and efficacy of marketed products in Kenya.

Name: ……

Signature: ……

Date: ……

Annex 14: The format and layout of the PSMF

The PSMF may be in electronic form on condition that a clearly arranged, printed copy can be made available to Board if requested. In any format, the PSMF should be legible, complete, provided in a manner that ensures all documentation is accessible and allow full traceability of changes. Therefore, it may be appropriate to restrict access to the PSMF in order to ensure appropriate control over the content and to assign specific responsibilities for the management of PSMF in terms of change control and archiving.

The PSMF should be written in English, indexed in a manner consistent with the headings described, and allow easy navigation to the contents. In general, embedded documents are discouraged. The use of electronic book-marking and searchable text is recommended. Documents such as copies of signed statements or agreements should be included as appendices and described in the index.
The documents and particulars of the PSMF shall be presented with the following headings and, if hardcopy, in the order outlined:

1. Cover Page

i. The unique number assigned by the electronic system or manually to the PSMF.
ii. The name of the MAH, the QPPV responsible for the pharmacovigilance system described (if different), as well as the relevant QPPV third party company name (if applicable).
iii. The name of other concerned MAH(s) (sharing the pharmacovigilance system).
iv. The list of PSMFs for the MAH (concerning products with a different pharmacovigilance system).
v. The date of preparation / last update.
vi. The qualified person responsible for pharmacovigilance, Annex A
vii. The list of tasks that have been delegated by the QPPV, or the applicable procedural document, Annex B
viii. The curriculum vitae of the QPPV and associated documents
ix. Contact details
x. The lists of contracts and agreements
xi. Sources of safety data, Annex C
xii. Lists associated with the description of sources of safety data e.g. affiliates and third-party contacts Computerised systems and Databases, Annex D, Pharmacovigilance Process, and written procedures, Annex E
xiii. Lists of procedural documents Pharmacovigilance System Performance, Annex F
xiv. Lists of performance indicators
xv. Current results of performance assessment in relation to the indicators Quality System, Annex G
xvi. Audit schedules
xvii. List of audits conducted and completed Products, Annex H
xviii. List(s) of products covered by the pharmacovigilance system
xix. Any notes concerning the MAH per product Document and Record Control,

Annex 1

xx. Logbook

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

The PSMF shall contain the following sections:

2. Qualified Person Responsible for Pharmacovigilance (QPPV)

The information relating to the QPPV provided in the PSMF shall include:

i. description of the responsibilities guaranteeing that the qualified person has sufficient control over the pharmacovigilance system in order to promote, maintain and improve compliance;
ii. a summary curriculum vitae with the key information on the role of the qualified person responsible for pharmacovigilance, including proof of registration in Kenya;
iii. contact details;
iv. details of back-up arrangements to apply in the absence of the qualified person responsible for pharmacovigilance;
v. A list of tasks that have been delegated by the qualified person for pharmacovigilance shall also be included in the Annexes.

The details provided in relation to the QPPV shall also include the description of the QPPV qualifications, experience and registrations relevant to pharmacovigilance. The contact details supplied should include name, postal address, telephone, fax and e-mail and represent the usual working address of the QPPV, which may therefore be different to a marketing authorization holder address. If the QPPV is employed by a third party, even if the usual working address is an office of the MAH, this should be indicated and the name of the company the QPPV works for provided.

3. Organizational Structure Of The Marketing Authorization Holder

A description of the organizational structure of the MAH relevant to the pharmacovigilance system must be provided. The description should provide a clear overview of the company(ies) involved, the main pharmacovigilance departments and the relationship(s) between organization s and operational units relevant to the fulfilment of pharmacovigilance obligations. This should include third parties. The PSMF shall describe:

i. The organizational structure of the MAH(s), showing the position of the QPPV in the organization.
ii. The site(s) where the pharmacovigilance functions are undertaken covering individual case safety report collection, evaluation, safety database case entry, periodic safety update report production, signal detection and analysis, risk management plan management, pre and post-authorization study management, and management of safety variations to product.
iii. Diagrams may be particularly useful; the name of the department or third party should be indicated.

4. Outsourced Activities

The PSMF, where applicable, shall contain a description of the activities and/or services subcontracted by the MAH relating to the fulfilment of pharmacovigilance obligations. This includes arrangements with other parties in any country, worldwide and if applicable, to the pharmacovigilance system applied to products authorized in Kenya.

Links with other organizations, such as co-marketing agreements and contracting of pharmacovigilance activities should be outlined. A description of the location and nature of contracts and agreements relating to the fulfilment of pharmacovigilance obligations should be provided. Individual contractual agreements shall be made available at the request of the Board or during inspection and audit and the list provided in the Annexes.

i. Sources of safety data

The description of the main units for safety data collection shall include all parties responsible, on a global basis, for solicited and spontaneous case collection for products authorized in Kenya. This shall include medical information sites as well as affiliate offices and may take the form of a list describing the country, nature of the activity and the product(s) (if the activity is product specific) and providing a contact point (address, telephone and e-mail) for the site. The list may be located in the Annexes of the PSMF. Information about third parties (license partners or local distribution/marketing arrangements) should also be included in the section describing contracts and agreements.

Flow diagrams indicating the main stages, timeframes and parties involved shall be used. However, the description of the process for ICSRs from collection to reporting to the Board should indicate the departments and/or third parties involved.

For the purposes of inspection and audit of the pharmacovigilance system, sources include data arising from study sources, including any studies, registries, surveillance or support programmes sponsored by the marketing authorization holder through which ICSRs could be reported. MAHs should be able to produce and make available a list of such sources to support inspection, audit and QPPV oversight. In the interests of harmonization, it is recommended that the list should be comprehensive for products authorized in Kenya, irrespective of indication, product presentation or route of administration. The list should describe, on a worldwide basis, the status of each study/programme, the applicable country (ies), the product(s) and the main objective. It should distinguish between interventional and non-interventional studies and should be organized per active substance.

The list shall be comprehensive for all studies/programmes and should include ongoing studies/programmes as well as studies/programmes completed in the last two years and may be located in an Annex or provided separately.

ii. Computerized systems and databases

The location, functionality and operational responsibility for computerized systems and databases used to receive, collate, record and report safety information and an

assessment of their fitness for purpose shall be described in the PSMF.
Where multiple computerized systems/databases are used, the applicability of these to pharmacovigilance activities should be described in such a way that a clear overview of the extent of computerization within the pharmacovigilance system can be understood. The validation status of key aspects of computer system functionality shall also be described; the change control, nature of testing, back-up procedures and electronic data repositories vital to pharmacovigilance compliance shall be included in summary, and the nature of the documentation available described. For paper-based systems (where an electronic system may only be used for expedited submission of ICSRs), the management of the data, and mechanisms used to assure the integrity and accessibility of the safety data, and in particular the collation of information about adverse drug events, shall be described.

iii. Pharmacovigilance processes

An essential element of any pharmacovigilance system is that there are clear written procedures in place. A description of the procedural documentation available (standard operating procedures, manuals), the nature of the data held (e.g. the type of case data retained for ICSRs) and an indication of how records are held (e.g. safety database, paper file at site of receipt) should be provided in the PSMF. A description of the process, data handling and records for the performance of pharmacovigilance, covering the following aspects shall be included in the PSMF:

a. Continuous monitoring of product risk-benefit profile(s) applied and the result of evaluation and the decision-making process for taking appropriate measures; this should include signal generation, detection and evaluation. This may also include several written procedures and instructions concerning safety database outputs, interactions with clinical departments etc.;
b. Risk management system(s) and monitoring of the outcome of risk minimization measures; several departments may be involved in this area and interactions should be defined in written procedures or agreements;
c. ICSR collection, collation, follow-up, assessment and reporting; the procedures applied to this area should clarify what are local and what are regional activities;
d. PSUR scheduling, production and submission
e. Communication of safety concerns to consumers, healthcare professionals and the Board;
f. Implementation of safety variations to the summary of product characteristics (SmPC) and patient information leaflets; procedures should cover both internal and external communications

In each area, the MAH should be able to provide evidence of a system that supports appropriate and timely decision making and action.
The description must be accompanied by the list of processes under the topic compliance management, as well as interfaces with other functions. Interfaces with other functions include, but are not limited to, the roles and responsibilities of the QPPV, responding to the Board's requests for information, literature searching, safety database change control, safety data exchange agreements, safety data archiving, pharmacovigilance auditing, quality control and training. The list, which may be located in the Annexes, shall comprise the procedural document reference

number, title, effective date and document type (for all standard operating procedures, work instructions, manuals etc.).
Procedures belonging to service providers and other third parties should be clearly identified. Documents relating to specific local/country procedures need not be listed, but a list may be requested on a per country basis. If no or only some countries use specific local procedures, this should be indicated (and the names of the applicable countries provided).

iv. Pharmacovigilance system performance

The PSMF should contain evidence of the ongoing monitoring of performance of the pharmacovigilance system including compliance of the main outputs of pharmacovigilance. The PSMF should include a description of the monitoring methods applied and contain as a minimum:

a. Assessment of correctness reporting of ICSRs is assessed. In the annex, figures/ graphs should be provided to show the timeliness of reporting over the past year;
b. Metrics used to monitor the quality of submissions and performance of pharmacovigilance. This should include information provided by NMRA authorities regarding the quality of ICSR reporting, PSURs or other submissions;
c. An overview of the timeliness of PSUR reporting to the Board (the annex should reflect the latest figures used by the marketing authorization holder to assess compliance);
d. An overview of the methods used to ensure timeliness of safety variation submissions compared to internal and the Board's deadlines, including the tracking of required safety variations that have been identified but not yet been submitted;
e. Where applicable, an overview of adherence to risk management plan commitments, or other obligations or conditions of marketing authorization(s) relevant to pharmacovigilance.
f. Targets for the performance of the pharmacovigilance system shall be described and explained. A list of performance indicators must be provided in the Annex to the PSMF alongside the results of (actual) performance measurements.

Annex 15: Format and content of the Protocol of Non-Interventional PASS and PAES

INTRODUCTION

The study protocol should be concise, while providing the information needed to understand how the study will answer the research question and assess the validity of the study design.

All headings and sub-headings of the format presented in this guidance should always be included and the same numbering should be used. Additional sub-headings can be added as necessary. Where a heading or sub-heading does not apply to the study (eg. Protection of human subjects), "Not applicable" should be stated with a short justification. All dates should be indicated in the format "DD Month YYYY" (e.g. 15 August 2018). Annex 1 should be used to list stand-alone documents not included in the protocol, e.g. contact details of responsible parties and all investigators, or sections 9.6. Data management, 9.8. Quality control and 10. Protection of human subjects, which can be maintained apart from the study protocol where they represent standard procedures applied to all studies. In this case, a summary should be provided in the corresponding section of the protocol and reference should be made to Annex 1. Annexes can be added to provide documents referred to in the protocol.

The text in green italics is intended to guide the reader on the principal points to be considered for writing that section of the protocol. It should be deleted if this guidance is used as a template.

It is reminded that the marketing authorization holder(s) involved should keep a copy of the protocol signed by the qualified person in pharmacovigilance (QPPV) or his/her delegate (with the date of the signature) available for any future request or inspection.

This guidance may be later revised based on experience.

1. **PASS/PAES information**: information should be provided in a table on the title page of the study protocol.

Title	Informative title including a commonly used term indicating the study design and the medicinal product, substance or drug class concerned
Protocol version identifier	Number
Date of last version of protocol	Date
Clinical trials registry reference number	Registration number in the clinical trials registry; indicate "Study not registered" if the study has not been registered
Active substance	List of pharmacotherapeutic group(s) (ACT codes) and active substance(s) subject to the study

Medicinal product	List of centrally authorized medicinal product(s) and/ or, if possible, of nationally authorized products subject to the study
Product reference	Reference number(s) of centrally authorized products and/or, if possible, of nationally authorized products subject to the study
Marketing authorization holder(s)	Marketing authorization holder(s) which initiate(s), manage(s) or finance(s) the study
Joint PASS	"Yes" or "No"
Research question and objectives	Summary of the research question and main objectives
Country(-ies) of study	List of countries where the study is to be conducted; if countries have not been identified yet, or if the list is not complete, this should be stated
Author	Name and contact details of the main author of the study protocol

2. Marketing authorization holder(s)

Marketing authorization holder(s)	Name, address and contact details of the marketing authorization holder(s).
MAH contact person	Contact person for this PASS protocol submission (if this a joint PASS, only one person should be mentioned)

3. Table of contents: (The study protocol should include a table of contents. The following table of contents can be used if this guidance serves as a template)

4. Responsible parties

(List of all main responsible parties, including the principal investigator, a coordinating investigator for each country in which the study is to be performed and other relevant study sites. Contact details and the list of all investigators can be kept in a stand-alone document to be listed in Annex 1 and to be available upon request.

In case of a Joint PASS, any sharing of responsibilities (eg. for management of adverse events) or distribution of tasks between marketing authorization holders and other responsible parties should be mentioned in this section. Contact persons for each marketing authorization holder should be mentioned.)

5. Abstract: (Stand-alone summary of the study protocol including all of the subsections below.)

i. Title: (The title should include subtitles including version and date of the protocol
ii. and name and affiliation of main author)

iii. Rationale and background Research question and objectives Study design. Population: ("Population" includes the setting and study population.)
iv. Variables Data sources Study size
v. Data analysis
vi. Milestones

6. Amendments and updates: (Write "None" or indicate any substantial amendment and update to the study protocol after the start of data collection in a table as indicated below.)

Number	**Date**	**Section of study protocol**	**Amendment or update**	**Reason**
1	Date	Text	Text	Text
2	Date	Text	Text	Text
…	Date	Text	Text	Text

7. Milestones: (Planned dates for study milestones should be indicated in a table as indicated below. Milestones between (< >) are optional and should be included only if applicable. Start of data collection and End of data collection are defined in Module VIII of the GVP (where the study uses data from existing electronic databases such as claims, prescriptions or health care records, "secondary use of data" applies to these definitions). Other important timelines can be added.)

8. 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.)

9. 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. Objectives should be organized as primary or secondary objectives where applicable.)

10. Research methods: Description of the research methods, including:

i. Study design: (Overall research design and rationale for this choice, specifying the study design proposed (cohort, case-control, etc.) and any comparison groups. The primary and secondary endpoints and the main measure(s) of effect should be mentioned. The strength of the study design to answer the research question may be explained in this section.)
ii. Setting: (Setting and study population defined in terms of persons, place, study time period, and selection criteria, including the rationale for any exclusion criteria and their impact on the number of subjects available for analysis. Plans for baseline visits and follow-up visits should be described. Representativeness of the study population as regards the source population should be addressed. Where any sampling from a source population is

undertaken, description of the source population and details of sampling methods should be provided. Where the study design is a systematic review or a meta-analysis, the criteria for the selection and eligibility of studies should be explained.)

iii. Variables: (Definition of exposures, outcomes, and other variables including measured risk factors, co-morbidities, co-medications, etc., with operational definitions and measurement; potential confounding variables and effect modifiers should be specified.

iv. Data sources: (Strategies and data sources for determining exposures, outcomes and all other variables relevant to the study objectives, such as potential confounding variables and effect modifiers. Where the study is based on secondary analysis an existing data source, such as electronic health records or claims databases, any information on the validity of the recording and coding of the data should be reported. For exposures or outcomes not previously validated, validation performed in the study should be described or otherwise addressed. Linkage methods between data sources should be described as appropriate. 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.)

v. 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. All assumptions used to calculate the study size or precision of the study should be presented and justified)

vi. Data management: Data management and statistical software(s) to be used in the study, including procedures for data collection, retrieval, collection and preparation. Data collection methods and tools (e.g. paper-based or electronic case reporting forms, monitoring if any and supervision) can be summarized in this section and fully described or presented in an Annex.

vii. Data analysis: Rationale for the choice of statistical techniques and major steps that lead from raw data to a final result, including methods used to correct inconsistencies or errors, impute values, modify raw data, categorize, analyze and present results, and procedures to control sources of bias and their influence on results. Statistical procedures to be applied to the data to obtain point estimates and confidence intervals of measures of occurrence or association, and sensitivity analyses.

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

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

x. Other aspects: Any other aspect of the research method not covered by the previous sections.

11. Protection of human subjects: Safeguards in order to comply with national and European Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.

12. Management and reporting of adverse events/adverse reactions: Procedures for the collection, management and reporting of individual cases of adverse events/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. For studies where reporting is not required, this should be stated. Any arrangements made between marketing authorization holders for the management and reporting of adverse events/reactions in Joint PASS should be specified.

13. Plans for disseminating and communicating study results: Any plans for submission of progress reports and final reports; any arrangements made between marketing authorizations holders for the disseminating and communicating study results of Joint PASS.

14. References: Numbered list of literature or electronic references of documents referred to in the protocol. Sufficient information should be provided to allow retrieval of the document. Feasibility or pilot studies that were carried out to support the development of the protocol, for example, the testing of a questionnaire or simple counts of medical events or prescriptions in a database to determine the statistical precision of the study, should be reported in the appropriate section of the study protocol with a summary of their methods and results. The full report should be made available to the Boardupon request. Feasibility or pilot studies that are part of the research process should be described in the protocol, for example, a pilot evaluation of the study questionnaire(s) used for the first set of patients recruited into the study.

15. 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.

Annex 16: Format of the PASS/PAES Final Study Report

1. **Title**: title including a commonly used term indicating the study design; sub-titles with date of final report and name and affiliation of main author. If the study has been registered in the clinical trials registry. Register, the final study report should mention on the title page "Register No:" with the registration number and the web link to the study record.
2. **Abstract**: The abstract of the final study report should include a summary of the study methods and findings.
3. **Marketing authorization holder**: name and address of the marketing authorization holder.
4. **Investigators**: names, titles, degrees, addresses and affiliations of the principal investigator and all co-investigators, and list of all collaborating primary institutions and other relevant study sites. Such information should be provided for each country in which the study is to be performed and other relevant study sites. A list of all collaborating institutions and investigators should be made available to the Agency and national competent authorities upon request.
5. **Milestones**: dates for the following milestones:
   i. Start of data collection (planned and actual dates)
   ii. End of data collection (planned and actual dates) or date of early termination, if applicable, with reasons for termination
   iii. Study progress report(s)
   iv. Interim report(s) of study results, where applicable
   v. Final report of study results (planned and actual date)
   vi. Any other important milestone applicable to the study, including date of study registration in the Register and date of protocol approval by an Institutional Review Board/Independent Ethics Committee if applicable.
6. **Rationale and background**: description of the safety concerns that led to the study being initiated or imposed, and critical review of relevant published and unpublished data evaluating pertinent information and gaps in knowledge that the study is intended to fill.
7. **Research question and objectives**: research question and research objectives, including any pre-specified hypotheses, as stated in the study protocol.
8. **Amendments and updates to the protocol**: list of any substantial amendments and updates to the initial study protocol after the start of data collection, including a justification for each amendment or update.
9. **Research methods:**
   9.1 **Study design**: key elements of the study design and the rationale for this choice.
   9.2 **Setting:** setting, locations, and relevant dates for the study, including periods of recruitment, follow-up, and data collection. In case of a systematic review or meta-analysis, study characteristics used as criteria for eligibility, with rationale.
   9.3 Subjects: any source population and eligibility criteria of study subjects. Sources and methods of selection of participants should be provided, including, where relevant methods for case ascertainment, as well as number of and reasons for dropouts.

9.4 Variables: all outcomes, exposures, predictors, potential confounders, and effect modifiers, including operational definitions and diagnostic criteria, if applicable.

9.5 Data sources and measurement: for each variable of interest, sources of data and details of methods of assessment and measurement. If the study has used an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data should be reported. In case of a systematic review or meta-analysis, description of all information sources, search strategy, methods for selecting studies, methods of data extraction and any processes for obtaining or confirming data from investigators.

9.6 Bias: any efforts to assess and address potential sources of bias at the design stage.

9.7 Study size: study size, rationale for any study size calculation and any method for attaining projected study size.

9.8 Data transformation: transformations, calculations or operations on the data, including how quantitative data were handled in the analyses and which groupings were chosen and why.

9.9 Statistical methods: description of the following items:

i. Main summary measures
ii. All statistical methods applied to the study, including those used to control for confounding and, for meta-analyses, methods for combining results of studies
iii. Any methods used to examine subgroups and interactions
iv. How missing data were addressed
v. Any sensitivity analyses
vi. Any amendment to the plan of data analysis included in the study protocol, with rationale for the change.

9.10 *Quality control*: mechanisms to ensure data quality and integrity.

10 *Results***:** presentation of tables, graphs, and illustrations to present the pertinent data and reflect the analyses performed. Both unadjusted and adjusted results should be presented. Precision of estimates should be quantified using confidence intervals. This section should include the following sub-sections:

10.1. *Participants*: numbers of study subjects at each stage of study, e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed, and reasons for non-participation at any stage. In the case of a systematic review or meta-analysis, number of studies screened, assessed for eligibility and included in the review with reasons for exclusion at each stage.

10.2. *Descriptive data*: characteristics of study participants, information on exposures and potential confounders and number of participants with missing data for each variable of interest. In case of a systematic review or meta-analysis, characteristics of each study from which data were extracted (e.g. study size, follow-up).

10.3. *Outcome data:* numbers of participants across categories of main outcomes.

10.4. *Main results*: unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). If relevant,

estimates of relative risk should be translated into absolute risk for a meaningful time period.

10.5. *Other analyses:* other analyses done, e.g. analyses of subgroups and interactions, and sensitivity analyses.

10.6. *Adverse events and adverse reactions*: summary of all adverse events/adverse reactions collected in the study, in line with requirements described set in these guidelines.

11 Discussion:

11.1. *Key results*: key results with reference to the study objectives, prior research in support of and conflicting with the findings of the completed post-authorization safety study, and, where relevant, impact of the results on the risk-benefit balance of the product.

11.2. *Limitations*: limitations of the study considering circumstances that may have affected the quality or integrity of the data, limitations of the study approach and methods used to address them (e.g., response rates, missing or incomplete data, imputations applied), sources of potential bias and imprecision and validation of the events. Both direction and magnitude of potential biases should be discussed.

11.3. *Interpretation*: interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies and other relevant evidence.

11.4. *Generalizability*: the generalizability (external validity) of the study results.

11.5. *Other information*: any additional or complementary information on specific aspects not previously addressed.

12 Conclusions: main conclusions of the study deriving from the analysis of the data.

Annex 17: Template for direct health care professional communication

<Date>

<Active substance, name of medicinal product and main message
*(e.g. introduction of a warning or a contraindication)***>**

Dear Healthcare professional,

<Name of marketing authorization holder> in agreement with <PPB> would like to inform you of the following:

Summary

Guidance: This section should be in bold/larger font size than the other sections of the DHCP and preferably in bullet points.

- <Brief description of the safety concern in the context of the therapeutic indication, recommendations for risk minimization (e.g. *contraindications, warnings, precautions of use)* and, if applicable, switch to alternative treatment>
- <Recall information, if applicable, including level (pharmacy or patient) and date of recall>

Background on the safety concern

Guidance: This section may include the following information:

<Brief description of the therapeutic indication of the medicinal product>

<Important details about the safety concern (adverse reaction, seriousness, statement on the suspected causal relationship, and, if known, the pharmacodynamics mechanism, temporal relationship, positive re-challenge or de-challenge, risk factors)>

<An estimation of the frequency of the adverse reaction or reporting rates with estimated patient exposure>

<A statement indicating any association between the adverse reaction and off-label use, if applicable>

<If applicable, details on the recommendations for risk minimization>

<A statement if the product information is to be or has been revised, including a description of the changes made or proposed> *Guidance: No need however to include or attach the precise (translated) text of the product information which, at the time of dissemination of the DHCP may not be available as final approved translations)*

<Place of the risk in the context of the benefit>

<The reason for disseminating the DHCP at this point in time>

<Any evidence supporting the recommendation (e.g. include citation(s) of key study/ies)>

<A statement on any previous DHCPs related to the current safety concern that have recently been disseminated>

<Any schedule for follow-up action(s) by the marketing authorization

holder/NMRA, if applicable>

Call for reporting
<A reminder of the need and how to report adverse reactions in accordance with the national spontaneous reporting system, including the details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system>

<For biological medicinal products, also include a reminder to report the product name and batch details>.

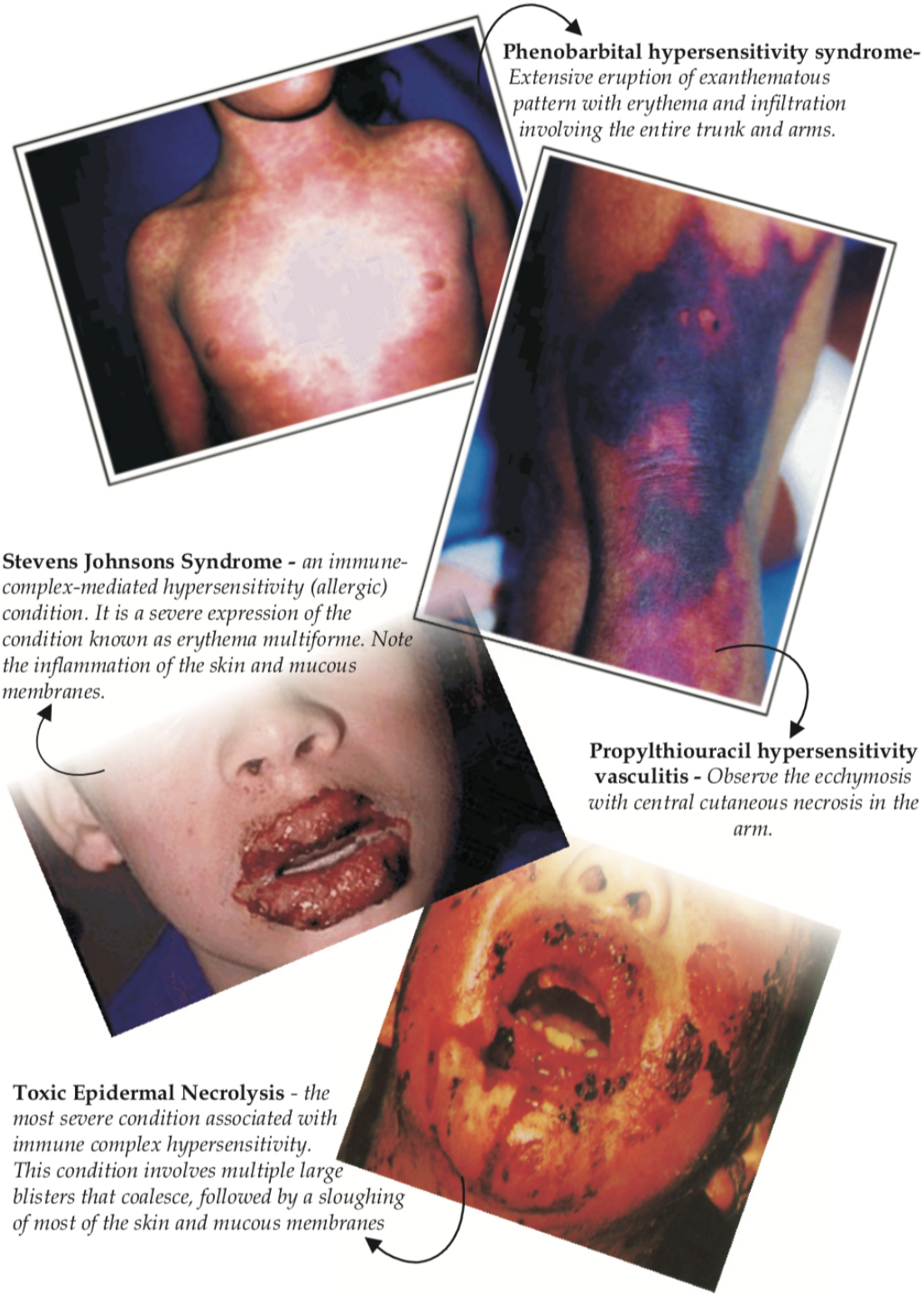
<Mention if product is subject to additional monitoring and the reason why>

Company contact point
<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

Annexes *(if applicable)*
<Link/reference to other available relevant information, such as information on the website of an NMRA>

<Additional scientific information, if applicable> <List of literature references, if applicable>

Pictorial representation of some well - known ADRs



Phenobarbital hypersensitivity syndrome- *Extensive eruption of exanthematous pattern with erythema and infiltration involving the entire trunk and arms.*

Stevens Johnsons Syndrome - *an immune-complex-mediated hypersensitivity (allergic) condition. It is a severe expression of the condition known as erythema multiforme. Note the inflammation of the skin and mucous membranes.*

Propylthiouracil hypersensitivity vasculitis - *Observe the ecchymosis with central cutaneous necrosis in the arm.*

Toxic Epidermal Necrolysis - *the most severe condition associated with immune complex hypersensitivity. This condition involves multiple large blisters that coalesce, followed by a sloughing of most of the skin and mucous membranes*

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