REPUBLIC OF RWANDA

RWANDA FDA
Rwanda Food and Drugs Authority

RWANDA FDA GUIDELINES ON SAFETY AND VIGILANCE OF MEDICAL PRODUCTS AND HEALTH TECHNOLOGIES

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FOREWORD

The Rwanda Food and Drugs Authority (RWANDA FDA) is a regulatory body established by the Law N° 003/2018 of 09/02/2018. One of the functions of RWANDA FDA is to regulate matters related to quality and safety of food for the purpose of protecting the public from health hazards associated with the consumption of medical products, especially in its article 8 paragraph 9.

These guidelines have been developed to provide guidance to the Rwanda Food and Drugs Authority (Rwanda FDA) and other stakeholders in carrying out safety and vigilance of medical products and health technologies. It is a domestication of EAC PV Compendium compiled by the Expert Working Group (EWG) on Pharmacovigilance of the East African Community Medicine Regulatory Harmonization (EAC MRH) Programme. The group relied on their experiences and knowledge on safety and vigilance of their individual Countries, and World Health Organization (WHO).

Rwanda FDA acknowledges all the efforts of key stakeholders who participated in the development and validation of these guidelines. These guidelines were developed in the spirit of EAC Member States medical products harmonization and domesticated in the alignment of our national requirements.

Director General
RWANDA FOOD AND DRUGSAUTHORITY

RESPONSIBILITY FOR IMPLEMENTATION OF THESE GUIDELINES

Rwanda FDA recognizes the work done by the EAC Secretariat in collaboration with the EAC Partner States National Medicines Regulatory Authorities(NMRAs) and the EAC harmonized guidelines have facilitated and contributed to the national domestication of the safety and vigilance of medical products and health technologies.This contributes to the uniformity in procedures for carrying out Pharmacovigilance activities, bring together regional expertise, promote learning, reliance and convergence, and reduce duplication of efforts and resources between Medicines Regulatory Authorities in the region.

Implementation of these guidelines will facilitate mutual recognition of regulatory decisions and assuranceof the quality and safety of medicines, cosmetics, medical devices and diagnostics manufactured, produced, imported, exported or traded in East African Community.

Rwanda FDA shall be responsible for the enforcement of these guidelines in Rwanda and also contribute to the regional harmonization initiatives for effective products quality and safety monitoring.

ABBREVIATIONS ANDACRONYMS

ADRs	Adverse Drug Reactions
AE	Adverse Event
AEFI	Adverse Events Following Immunization
ART	Assisted Reproductive Technology
BCG	Bacillus Calmette-Guerin
CEM	Cohort Event Monitoring
CIOMS	Council for International Organizations of Medical Sciences
DEC	Drug Event Combination
DIBD	Development International Birth Date
DME's	Designated Medical Events
DSURs	Development Safety Update Reports
EAC	East African Community
eCTD	Electronic Common Technical Document
EMA	European Medicines Agency
EMEA	Europe, Middle East and Africa
FSN	Field Safety Notices
FSCA	Field Safety Corrective Actions
GVP	Good Pharmacovigilance Practices
HLT	High Level Term (in MedDRA)
IBD	International Birth Date
ICH	International Council on Harmonization
ICSR	Individual Case Safety Reports
IME's	Important Medical Events
ISO	International Organization for Standards
IT	Information Technology
IVD	In-Vitro Diagnostics
IVF	In-Vitro Fertilization
LTR	Local technical representative

MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Drug Regulatory Authorities
NMRAs	National Medical Regulatory Authority
NPC	National Pharmacovigilance Centre
PAC	Pharmacovigilance Advisory Committee
PASS	Post Authorization Safety Studies
PBRER	Periodic Benefit Risk Evaluation Report
PHP	Public Health Programs
PL	Patient Leaflet
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PSAC	Pharmacovigilance Safety Advisory Committee
PT	Preferred Term
PV	Pharmacovigilance
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
SAE	Serious Adverse Event
SDA	Signal Detection Algorithm
SDR	Signal of Disproportionate Reporting
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SUSARs	Suspected Unexpected Serious Adverse Reactions
WHO	World Health Organization

GLOSSARY OF TERMS

In the context of these guidelines the following words/phrases are defined as follows.

Abnormal use

Act or omission of an act by the operator or user of a medical device as a result of conduct that is beyond any reasonable means of risk control by the manufacturer.

Active surveillance

Active measures are taken to find adverse events (e.g. cohort event monitoring).

Accuracy

The accuracy of an analytical procedure expresses the closeness of agreement between the value, which is accepted either as a conventional true value or an accepted reference value and the value found.

Adverse Drug Reactions (ADRs)

A response to a medicine which is noxious and unintended, and which occurs at a dose normally used in human for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function. The term adverse drug reaction should be considered for harmful or seriously unpleasant effects occurring at doses intended for therapeutic, prophylactic or diagnostic effect and which calls for reduction of dose or withdrawal of the medicine and/or forecast hazard from future administration.

Adverse Event (AE)

Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of the product whether or not related to the product. For the purposes of this compendium, adverse events will cover adverse drug reactions, adverse events following immunizations and incidences following the use of a medical device.

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 unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.

AEFIs are grouped into five categories:

Cause-specific type ofAEFI	Definition
Vaccine product-related reaction	An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product and occurs even when the vaccine has been prepared, handled and administered correctly. e.g. pain, swelling, redness following BCG vaccination
Vaccine quality defect-related reaction	An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defect of the vaccine product, including its administration device as provided by the manufacturer, e.g. Failure by the manufacturer to completely inactivate a lot of inactivated polio vaccine leads to cases of paralytic polio
Immunization error-related reaction (formerly "Programme error")	An AEFI that is caused by in appropriate vaccine handling, prescribing or administration and thus by its nature is preventable. E.g. Transmission of infection by contaminated multi dose vial. Deaths associated with the reconstitution of vaccines with an incorrect diluent or a drug
Immunization anxiety-related reaction	An AEFI arising from anxiety about the immunization. These reactions are not related to the vaccine, but to fear of the injection. E.g. Vasovagal syncope or fainting in an adolescent during/following vaccination.
Coincidental event	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety, but a temporal association with immunization exists. E.g. A fever occurs at the time of the vaccination (temporal association but is in fact caused by malaria

Analytical sensitivity

Analytical sensitivity measures a test's ability to detect a low concentration of a given substance. Sometimes used interchangeably as limit of detection or detection limit.

Become aware

Manufacturers are considered to have "become aware" of a reportable event when: (1) any employee becomes aware of are portable event or (2) any employee who is a person with management or supervisory responsibilities over persons with regulatory, scientific or technical

responsibilities, or a person whose duties relate to the collection and reporting of adverse events, becomes aware that a reportable event, from any source, including any trend analysis, necessitates remedial action to prevent an unreasonable risk of substantial harm to public health.

Case-Control Studies

Studies used to validate signals and to identify risk factors for adverse events (establishing association between medicine and one specific rare adverse event).They compare two groups: those with a condition (event) under study (cases) and a similar group which do not have the condition (controls) by looking backwards in time (retrospectively) to measure the exposure status of the two groups (to the medicine) and compare the relative risk of developing the condition in the two groups.

Causal association

A cause-and-effect relationship between a causative factor and a disease with no other factors intervening in the process.

Clinical sensitivity

The number of true positive specimens identified by a given assay as positive divided by the number of specimens identified by the reference assays as positive, expressed as a percentage.

Clinical specificity

The number of true negative specimens identified by a given assay as negative, divided by the number of specimens identified by the reference assays as negative, expressed as a percentage.

Cluster

Two or more cases of the same event or similar events related in time, geography, and/or the vaccine administered. National Programme managers may decide upon a more precise definition.

Coincidental event

An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.

Conformity

Fulfillment of a requirement.

Conformity assessment

The systematic examination of evidence generated and procedures undertaken by the manufacturer, under requirements established by the Rwanda FDA, to determine that a medical device is safe and performs as intended by the manufacturer and, therefore, conforms to the Essential Principles of Safety and Performance of Medical Devices.

Component Complaint

Any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device.

Correction

Action to eliminate a detected nonconformity.

Corrective action

Action to eliminate the cause of a detected non-conformity or other undesirable situation and to prevent recurrence.

Cohort Event Monitoring (CEM)

A system created to actively monitor drug events in a population. Healthcare providers are requested to report all clinical events, regardless of whether they are suspected adverse reactions, for identified patients receiving a specified drug.

Data mining

A field at the intersection of computer science and statistics that attempts to discover in apparent patterns in large data sets. Data mining utilizes methods at the intersection of artificial intelligence, machine learning, statistics and database systems. The overall goal of the data mining process is to extract information from a data set and transform it into an understandable structure for further use.

Drug Utilization Studies

Studies designed to describe how a medicine is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes.
They can be used to determine rates and to describe the effect of regulatory actions and media attention on the use of medicines, as well as to develop estimates of the economic burden of the cost of medicines as well as compare recommended and actual clinical practice.

External quality assessment

Monitoring of performance through either direct observation and supervision or inter-laboratory

comparisons made possible by participation in an external quality assessment scheme (sometimes known as proficiency testing).

Falsified vaccines

Vaccines that deliberately/fraudulently misrepresent their identity, composition or source

Field safety corrective action (FSCA)

Action taken by the 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.

Field safety notice (FSN)

A communication sent out by the manufacturer or its representative to the device users in relation to a field safety corrective action.

Haemovigilance

The WHO defines hemovigilance as set of surveillance procedures covering the entire blood transfusion chain, from the donation and processing of blood and its components, through 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.

Harm

Physical injury or damage to the health of people or damage to property or the environment.

Hazard

Potential source of harm.

Health care providers

For the purposes of reporting suspected adverse reactions, health care providers are defined as medically qualified persons, such as physicians, dentists, pharmacists, nurses, assistant medical officers and clinical officers, pharmaceutical technicians, pharmaceutical assistants and traditional medicine practitioners.

Herbal medicines

Includes herbs (e.g. crude plant materials such as leaves, flowers, fruit, seed etc.), herbal materials

(e.g. fresh juices, gums, fixed oils, essential oils, dry powders etc.), herbal preparations (e.g. comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials)and finished herbal products(e.g. dosage forms preparations made from one or more herbs, may contain excipients etc.).

Immunization anxiety-related reaction

An AEFI arising from anxiety about the immunization.

Immunization error-related reaction (formerly programmatic error)

An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus, by its nature, is preventable.

Immunization safety

The public health practices and policies dealing with the various aspects of the correct administration of vaccines, focusing on minimizing the risk of transmission of disease with the injection and maximizing the effectiveness of the vaccine. The term encompasses the spectrum of events from proper manufacture to correct administration.

International Birth Date (IBD)

A document providing the most complete information related to an individual case at a certain point in time. An individual case is the information provided by a primary source to describe suspected adverse reaction(s) related to the administration of one or more medicinal products to an individual patient at a particular point in time.

In vitro diagnostic (IVD)

A 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. This includes reagents, calibrators, control materials, specimen receptacles, software and related instruments or apparatus or other articles.

Lack of Efficacy

Un expected failure of a drug to produce the intended effect as determined by previous scientific investigations.

Lot/Batch

Defined amount of material, either starting material, intermediate or finished product which is uniform in its properties and has been produced in one process or series of processes.

Local technical representative

A person or company appointed by the manufacturer or the Marketing Authorization Holders to import, receive as donation, distribute or sell a medicinal product.

Manufacturer

The natural or legal person responsible for design, production, assignment of intended purpose, packaging and labeling of the diagnostic product whether these tasks are performed by that person or on their behalf and who represent themselves as the manufacturer on the diagnostic product labeling.

Marketing Authorization Holder (MAH)

An individual or a corporate entity responsible for placing a pharmaceutical product in the market.

Medical device

Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease, diagnosis, monitoring, treatment, alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;
- investigation, replacement or modification of the anatomy or of a physiological process;
- control of conception;

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

Medical product

Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or making a medical diagnosis

Medication error

Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures and systems, including prescribing; order communication; product labeling, packaging and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Authority

The authority refers to Rwanda Food and Drugs Authority "Rwanda FDA", the competent authority having mandate to regulate food and drugs.

National Pharmacovigilance Centre (NPC)

A single, recognized center (or integrated system) within a Rwanda FDA with the clinical and scientific expertise to collect, collate, analyze and give advice on all information related to drug safety.

National Reference Laboratory (NRL)

A testing laboratory which in agreement with a specified laboratory community or through appointment by a competent organization provides reference values in a specific technical field, i.e. property values of materials or products to which test results can be related or traced back and whose quality is fit for the purpose.

Nonconformity

Non-fulfillment of a requirement.

Over dosage

A drug overdose is the accidental or intentional use of a drug or medicine in an amount that is higher than is normally used.

Periodic Safety Update Report (PSUR)

An update of the world-wide safety experience of a product obtained at defined times post marketing authorization. A Periodic Safety Update Report (PSUR) is a pharmacovigilance document intended to provide an evaluation of the risk-benefit balance of a medicinal product at defined time points post-authorization.

Pharmacovigilance (PV)

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible medicine-related problems.

Preventive action

Action to eliminate the cause of a potential nonconformity or other undesirable situation and to prevent occurrence.

Requirement

Need or expectation that is stated, generally implied or obligatory.

Risk

Combination of the probability of occurrence of a harm and the severity of that harm.

Risk-Benefit Balance

An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks (any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health

Risk Management System

A risk management system comprise a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, including the assessment of the effectiveness of those interventions.

Risks related to use of a medicinal product

Any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health and any risk of undesirable effects on the environment.

Sample

One or more units of product, either components or finished devices, drawn from a lot without regard to the quality of the units.

Sample size

Number of units of product in the sample.

Serious Adverse Event (SAE) or Serious Adverse Drug Reactions (Serious ADR)

Serious adverse reaction means an adverse reaction which results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.
Life threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.
Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above.
Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Side effect

Any unintended effect of a pharmaceutical product occurring at doses normally used in man, which is related to the pharmacological proprieties of the drug.

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 information.

Signal management process

A set of activities performed to determine whether, based on an examination of individual case safety reports, aggregated data from active surveillance systems or studies, scientific literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed, as well as any relatedrecommendations, decisions, communications and tracking.

Spontaneous reporting

An un solicited communication of suspected adverse reactions by a healthcare provider or consumer to a company, Rwanda FDA or other organization which fulfills the following three conditions:

a) it describes one or more suspected adverse reactions in a patient
b) The patient was given one or more medicinal products
c) it does not derive from a study or any organized data collection scheme.

Substandard vaccines

Authorized vaccines that fail to meet either their quality standards or specifications.

Summary Product Characteristics (SmPC)

Product information as approved by Rwanda FDA. The SmPC serves as the basis for production of information for healthcare providers as well as for consumer information on labels and leaflets of medicinal products.

Surveillance

Continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice.

Test kit

Commercially prepared reagent sets, with accessory devices, containing all of the major components and literature necessary to perform one or more designated diagnostic tests or procedures.

Testing algorithm

A testing algorithm describes the combination and sequence of specific HIV assays used within a given HIV testing strategy.

Testing strategy

Generic description of a testing approach for a specific need (for example, blood transfusion and transplantation safety, HIV surveillance, and/or diagnosis of HIV infection in both client-initiated and provider-initiated testing and counseling), taking into consideration the presumed HIV prevalence in the population being tested.

Toxicity

Cell damage from a direct action of the medicine, often at a high dose, e.g. liver damage from paracetamol overdose.

Trend reporting

A reporting type used by the manufacturer when a significant increase in the events not normally considered to be incidents occurred and for which pre-defined trigger levels are used to determine the threshold for reporting.

Unexpected Adverse Drug Reaction

An adverse reaction, the nature, severity or outcome of which is not consistent with domestic labeling, marketing authorization or the Summary of Product Characteristics (SmPC). This includes class-related reactions which are mentioned in the SmPC but which are not specifically described as occurring with this product.

Unanticipated

A death or serious injury is considered unanticipated if the condition leading to the event was not considered in a risk analysis performed during the design and development phase of the device. There must be documented evidence in the design file that such analysis was used to reduce the risk to an acceptable level.

Vaccination failure

Vaccination failure is based on clinical endpoints or immunological criteria, where correlates or surrogate markers for disease protection exist. Vaccination failure can be due to vaccine failure (either "primary" when immune response is inadequate or "secondary" when the immune response wanes) or failure to vaccinate (i.e. when an indicated vaccine was not administered appropriately for any reason).

Vaccine pharmacovigilance

The science and activities relating to the detection, assessment, understanding and communication of AEFI and other vaccine or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.

Vaccine product

All components of a given vaccine formulation, including the immunogen (part of the vaccine that stimulates an immune response) and others that may be present such as the adjuvant, preservative and other additives used during the manufacturing process to confirm product quality/stability (e.g. potassium or sodium salts, albumin, gelatin), support growth and purification of specific immunogens (e.g. egg or yeast proteins, antibiotic) or inactivate toxins (e.g. formaldehyde).

Vaccine product-related reaction

An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product, whether the active component or one of the other components of the vaccine (e.g. adjuvant, preservative or stabilizer).

Vaccine quality defect-related reaction

An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer.

Verification

Confirmation, through the provision of objective evidence, that specified requirements have been fulfilled.

Vigiflow

A web-based data management tool used to manage ADR database. All data are stored on a database server in Uppsala, Sweden.

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

Evidence of the risks and benefits of drugs and vaccines continue to emerge over the lifecycle of the product. The post-market uncertainties concerning the benefits and risks of a drug or vaccine extend beyond its inherent properties. The incidence, risk factors, and severity of reactions to a drug or vaccine in one population may differ significantly from another based on environmental and genetic reasons that can be difficult to predict. Programmatic errors occur in prescribing, preparing, administering, or taking medicines.

Pharmacovigilance is an arm of patient care and aims at identify new information about hazards, prevent harm to patients and getting the best outcome of treatment with medicines and other products. The science allows identification, assessment and understanding of risks including risk factors when medicines are used after marketing authorization and also enables measures to be taken to prevent adverse reactions to patients.

There are two major approaches in pharmacovigilance – spontaneous or passive reporting and active surveillance systems. Passive reporting means that no active measures are taken to find adverse effects other than the encouragement of healthcare providers and others to report safety concerns. Passive reporting is voluntary and depends on the initiative and motivation of the reporter(s). Active (or pro-active) surveillance means that active measures are taken to find adverse events.

Information from spontaneous adverse drug reactions post authorization clinical trials, case-control studies and other post market studies are used to aid decision making. The information from these sources may lead to changes in product labels, restriction on product use, strengthening of specific warning or may lead to product withdraw.

Pharmacovigilance systems are being implemented in Rwanda since 2009. The systems are still being strengthened under the mandate of Rwanda FDA.
However, the current existing pharmacovigilance system in Rwanda are at different levels of public health facilities. Very few reports have been collected and following the ongoing efforts in Rwanda to strengthen medicines safety.

The guidelines provide the requirements, procedures, roles and activities in pharmacovigilance, for public health programs (HIV, TB, Malaria, Expended Program for Immunization, Maternal and Child Health program, NCDs etc), Ministry of Health, Marketing Authorization Holders (MAH), Academia, research institutions, advisory committees, Local Technical representatives (LTR), Rwanda FDA health facilities, health workers, patients/consumers and other stakeholders.

The guidelines therefore outline the reporting requirements for the different stakeholders, data management, and communication, training requirements as well as monitoring and evaluation of

pharmacovigilance systems.It further highlights requirements for expedited reporting, reporting of unusual failure in efficacy, medication errors and suspected poor quality medical products.
Various tools for collection of data including reporting forms have also been appended with the guidelines for easy referencing.

1.2 POLICY AND LEGAL FRAMEWORK OF PHARMACOVIGILANCE

Harmonization of Pharmacovigilance guidelines is an explicit policy priority under Chapter 21 (Article 118) of the EAC Treaty and vital in enabling the free movement of goods in line with the EAC Common Market Protocol. Streamlining pharmacovigilance requirements and practices both at Regional and national level will have a positive impact to public health by increasing access to good quality, safe and efficacious medicines. The Health sector policy of January 2015 provides for the establishment and strengthening of a pharmacovigilance system within healthcare facilities.

The Pharmacy policy published in April 2016, provides for the strengthening health products information and pharmacovigilance system which requires for a well designed and coordinated system for effective implementation of these guidelines.
The law No 003/2018 of 09/02/2018 establishing Rwanda Food and Drugs Authority, especially in its article 8, paragraph 9, Rwanda FDA is mandated to conduct pharmacovigilance and post marketing surveillance
The existing legal framework, also mandate the marketing authorization holders (MAH), Local Technical Representatives and (or) pharmaceutical manufacturers to continuously monitor and report safety of products that they are responsible for on the market.
There are different approaches for reporting and monitoring adverse events and/or reactions. Amongst them include spontaneous reporting system, active surveillance system (e.g. cohort event monitoring pregnancy register, case-control studies, drug utilization studies etc.) and Rwanda FDA will oversee the enforcement of such provisions

CHAPTER 2: PHARMACOVIGILANCE SYSTEMS

The Pharmacovigilance system is composed of structures, processes, resources, documentation and outcomes of pharmacovigilance activities and is designed to monitor the safety of medical products and health technologies. The aim is to promote safe and effective use of the products and timely provision of safety information to ensure that consumers of medical products are prevented from any harm that may arise from their use. Pharmacovigilance system is used by Rwanda FDA, Manufacturers, Market Authorization Holders, health facilities, Public Health Programs, suppliers, Ministry of Health (MoH), Research institutions, Contract research Organizations (CROs), professional bodies/councils, academia, distributors and several other stakeholders of regulated products to fulfill their obligations towards patient and public safety.

2.1 PRINCIPLES FOR GOOD PHARMACOVIGILANCE PRACTICES (GVP)

Pharmacovigilance stakeholders are expected to adhere to the following principles of good pharmacovigilance practices to guide the design of all structures and processes as well as the conduct of all tasks and responsibilities:

1. The needs of patients, healthcare professionals and the public in relation to the safety of medical products and health technologies should be met.
2. Upper management should provide leadership in the implementation of the quality system and motivation for all staff members in relation to the quality objectives.
3. All persons within the organization should be involved in and support the pharmacovigilance system on the basis of task ownership and responsibility in a degree according to their tasks and assigned responsibilities.
4. All persons within the entire organization should engage in continuous quality improvement.
5. Resources and tasks should be organized as structures and processes in a manner that will support the proactive, risk-proportionate, continuous and integrated conduct of pharmacovigilance.
6. All available evidence on the risk-benefit balance of medicinal products should be sought and all relevant aspects, which could impact on the risk-benefit balance and the use of a product, should be considered for decision-making.
7. Good cooperation should be fostered between marketing authorization holders, Rwanda FDA, public health Programmes, patients, healthcare professionals, communities and other relevant stakeholders.

2.2FACILITIES AND EQUIPMENT FOR PHARMACOVIGILANCE

Appropriate facilities and equipment shall be allocated to support pharmacovigilance processes and their outcomes. These shall include but not limited to office space, information technology (IT)

systems and (electronic) storage space.

The facilities should be located, designed, constructed, adapted and maintained to suit their intended purpose in line with the quality objectives for pharmacovigilance. Facilities and equipment which are critical for the conduct of pharmacovigilance should be subject to periodic appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose.

2.3QUALITY SYSTEMS

The pharmacovigilance system requires robust quality control and assurance system that covers the organizational structure, responsibilities, procedures, processes and resources. This system is essential for monitoring and evaluation as well as appropriate resource management, compliance management and record management as required by the current international quality standard.

The Pharmacovigilance stakeholders shall be required to establish a quality system for all pharmacovigilance activities to produce desired outcome and quality objectives. The Pharmacovigilance quality system shall involve quality planning, adherence, control, assurance and improvements.
A description of the quality management system should be provided, in terms of the structure of the organization and the application of the quality to pharmacovigilance. This shall include: quality documentation, record management, training of personnel in pharmacovigilance, communication and continuous improvement.

2.4QUALITY DOCUMENTATION AND RECORD MANAGEMENT

Implementation of pharmacovigilance activities shall follow quality system documentation in accordance with Rwanda FDA quality management system.Pharmacovigilance information shall be recorded, handled and stored so as to allow accurate reporting, interpretation and verification.

A record management system shall be established for all documents used for pharmacovigilance activities to ensure that they are easily retrievable and traceable. The records shall include measures taken to investigate safety concerns, timelines taken for the investigations and the decision-making process.

Pharmacovigilance records management system shall ensure that the data is complete, accurate and of high integrity. The data shall be timely accessible. The retention of pharmacovigilance data and documents relating to registered medicinal products shall be for at least 10 years after the marketing authorization has ceased to exist.

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

The retention of minimum elements of the pharmacovigilance system master file (PSMF) shall be as long as the system described in the PSMF exists and for at least further 5 years after it has been formally terminated by the marketing authorization holder and/or LTR. Measures shall be in place to ensure that confidentiality of the data is maintained, access to the data is restricted and data is protected from destruction.

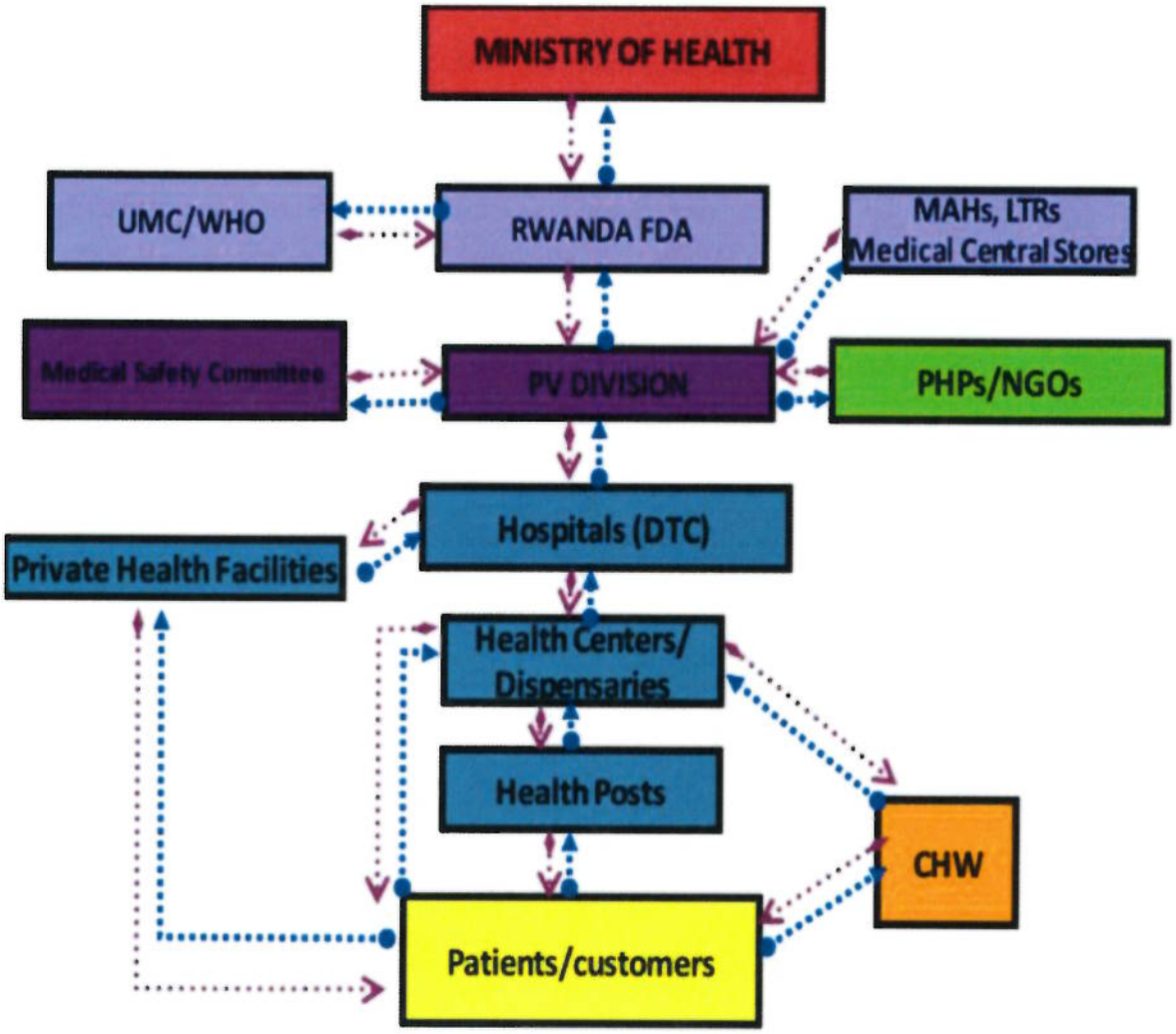
2.5TRAINING OF PERSONNEL FOR PHARMACOVIGILANCE

Institutions involved in pharmacovigilance activities shall ensure availability of a sufficient number of competent and appropriately qualified and trained personnel to perform Pharmacovigilance activities. This includes not only staff within the pharmacovigilance units but also staff who may receive or process safety reports, such as sales personnel or clinical research staff. The institution shall also establish a training system on vigilance with adequate documentation such as training plans, training records, curricula vitae and job descriptions

2.6. COMMUNICATIONS WITHIN PHARMACOVIGILANCE STAKEHOLDERS

Communication system shall be established to facilitate timely interaction among Pharmacovigilance stakeholders.

The flow chartof information and feedback are as follows:



CHAPTER 3: PHARMACOVIGILANCE PROCESSES, ROLES& RESPONSIBILITIES

3.1 PHARMACOVIGILANCE PROCESSES

Rwanda FDA has established a pharmacovigilance system for the collection and evaluation of information relevant to the risk-benefit balance of medical products and health technologies in accordance with Health Sector Policy 2015. Rwanda FDA shall continuously monitor the safety profile of the products marketed in Rwanda and take appropriate action where necessary and monitor the compliance of MAHs with their obligations with respect to pharmacovigilance. Rwanda FDA shall ensure that all stakeholders implement, when appropriate, Risk Management Plans to effectively monitor and manage risks associated with the safety of medical products and health technologies.

For a functional pharmacovigilance system, the following processes are critical:

1. Continuous safety profile monitoring and benefit-risk evaluation of authorized medical products and health technologies;
2. Establishing, assessing and implementing risk management systems and evaluating the effectiveness of risk minimization;
3. Collecting, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of safety reports from any source;
4. Signal management;
5. Scheduling, preparation (including data evaluation and quality control), submission and assessment of periodic safety update reports;
6. Meeting commitments and responding to requests from Rwanda FDA and/or stakeholders including provision of correct and complete information;
7. Interaction between the pharmacovigilance and product quality defect systems;
8. Communication about safety concerns between marketing authorization holders and Rwanda FDA, in particular notifying changes to the risk-benefit balance of medicinal products;
9. Communicating information to patients and healthcare professionals about changes to the risk-benefit balance of products for the aim of safe and effective use of medicinal products;
10. Keeping product information up-to-date with the current scientific knowledge, including the conclusions of the assessment and recommendations.
11. Implementation of variations to marketing authorizations for safety reasons according to the urgency required.

3.2ROLES AND RESPONSIBILITIES

3.2.1 Rwanda FDA/Division of Pharmacovigilance and Food Safety Monitoring

Rwanda FDA through the dedicated division of PV and Food Safety monitoring shall play the role of National Pharmacovigilance center and shall have the following responsibilities:

a) Coordinating pharmacovigilance activities in Rwanda,
b) Planning and budgeting for national pharmacovigilance activities,
c) Developing, reviewing and distributing AE forms and collecting reports of suspected adverse reactions to medicinal products and health technologies,
d) Acknowledging receipt of AE reports from health care providers, health facilities, PHPs, CROs, MAHs/LTRs, regional and international medicine regulatory authorities and other PV stakeholders,
e) Conducting causality assessment and analyzing adverse reactions reports,
f) Generating hypotheses or identifying signals and taking appropriate regulatory action(s) based on signals generated,
g) Collecting and communicating relevant safety information to all stakeholders,
h) Linking with WHO program for international drug monitoring and sharing information on adverse reactions,
i) Providing feedback to reporters including alerting prescribers, health facilities, PHPs, MAH/manufactures/LTR and the public to new risks of adverse reactions,
j) Issuing ADR Bulletins/Newsletters, Health professional letters, etc
k) Conducting pharmacovigilance inspection at the MAHs/local manufacturers/LTR facilities, health facilities, public health programs, and CROs
l) Monitoring and evaluating all pharmacovigilance activities in Rwanda.
m) Conducting trainings and sensitization of different pharmacovigilance stakeholders.
n) Coordinate in-service Pharmacovigilance educational activities for healthcare providers and consumers
o) Taking regulatory action on a particular medical products and health technologies with serious adverse reaction/event,
p) Responding to queries and providing information related to pharmacovigilance activities to relevant stakeholders,
q) Reviewing ADR reports and feeding information into the data management tool–Vigiflow where accessible and share them with EAC Partner States NMRAs for further action when necessary,
r) Receiving safety alerts from national and international sources and sharing them with health care providers, patients and other relevant stakeholders
s) Collaborate with the respective pharmacovigilance stakeholders in implementing pharmacovigilance activities,
t) Reviewing risk management plans,
u) Ensuring compliance to the good pharmacovigilance practices,

v) Collaborate with medical training institutions to incorporate pharmacovigilance module in the curriculum,
w) Conduct active surveillance on safety issues in Rwanda in partnership with PHPs and/or other relevant stakeholders,
x) Conduct and promote research related to pharmacovigilance activities
y) Serve as the secretariat of the Pharmacovigilance Advisory Committee (PAC)
z) Follow up on implementation of feedback/regulatory action taken for safety reasons on medical products.

3.2.2 Pharmacovigilance Advisory Committee

The Pharmacovigilance Advisory Committee will assess scientific, safety and pharmacovigilance documentation on individual medical products and health technologies giving recommendations and advice on Rwanda FDA concerns. The roles and responsibilities of the advisory committees include the following:

a) Provide guidance on risk management of the use of medical products including the detection, assessment, minimization and communication relating to the risk of adverse reactions, the design and evaluation of clinical trials, post-authorization safety studies (PASS) and pharmacovigilance audit/inspections,
b) Provide recommendations for urgent safety procedures,
c) Assess post-authorization safety studies protocols and issue recommendations,
d) Evaluate and issue recommendations on signals,
e) Provide advice for updating medical products list with safety concerns requiring additional monitoring,
f) Provide recommendation for Risk management plans (RMP),
g) Advice on safety consideration for the medical products which undergo a renewal and/or for safety variations,
h) For Rwanda FDA safety announcements and communications: the advisory committee shall issue an advice on the timing and message content for individual safety cases.

3.2.3 Public Health Programs

Public Health Programs (PHP) such as HIV/AIDS, TB, Malaria, Expended Program on Immunization, Maternal and Child Health program, NCDs etc.) shall be actively engaged in pharmacovigilance activities with the following roles and responsibilities:

a) Include and budget for pharmacovigilance activities in their strategic plan,
b) Develop pharmacovigilance plan for medical products used by the programs
c) Have a focal person (pharmacist or medical doctor), to coordinate PV activities in collaboration with Rwanda FDA,
d) Distribute reporting forms (ADR, Patient Alert Cards, suspected poor quality reporting forms) in Programme sites,
e) Collect data using appropriate reporting forms,

f) Collaborate with Rwanda FDA/PV-SM Division on active surveillance of their products,
g) Develop risk management plans and follow-up patients,
h) Train health care providers in reporting adverse drug events including other aspects of pharmacovigilance,
i) Promote rational and safe use of medical products by health care providers,
j) Educate and inform patients on the importance of reporting adverse drug events,
k) Assess and communicate risks and effectiveness of medicines used in the specific PHP in collaboration with Rwanda FDA/PV-SM Division,
l) Develop protocols and conduct active surveillance of medical products used in the program
m) Monitor and evaluate the impact of pharmacovigilance interventions.
n) Provide medicine safety information during the launch of new drug regimens;
o) Put in place a mechanism to disseminate Safety information to health professionals and the general public,
p) Conduct surveys and research on safety of medical products used in program
q) Responding to rumours and managing crises as necessary regarding to the safety of medical products used in the problem,
r) Implement feedback/regulatory action taken for safety reasons on medical products,

3.2.4Health Facilities

Public and private health facilities shall have the following roles and responsibilities in Pharmacovigilance:

a) Allocate budget for pharmacovigilance activities,
b) Receive and distribute ADR reporting forms to health care providers,
c) Sensitize healthcare providers on Pharmacovigilance activities
d) Detect, investigate, manage and report ADRs and take appropriate action to prevent ADRs,
e) Communicate appropriate safety information to health care providers and the community including patients,
f) Identify focal person to coordinate pharmacovigilance activities within health facility,
g) Maintain a register of suspected ADRs including medication errors.
h) Moreover, public and private hospitals shall establish a functional Drugs and Therapeutic Committees (DTCs) with a PV subcommittee with following roles and responsibilities:
i) Ensure the proper use of the adverse event notification forms and patient alert cards in health facilities
j) Ensure that healthcare providers are trained and familiar with the completion of the reporting forms and patient alert cards
k) Collect, validate and transmit all reporting forms to Rwanda FDA/PV-SM Division
l) Conducting causality assessment and analyzing adverse reactions reports from health facility and catchment area,
m) Conduct preliminary identification of signals and other risk factors,
n) Organize and conduct staff training and sensitization on matters related to pharmacovigilance,

o) Identify and suggest interventions to address any medicine safety and/or irrational use issues in health facilities within their catchment area
p) Implement feedback/regulatory action taken for safety reasons on medical products,

3.2.5 Marketing Authorization Holders, Manufacturers, Local Technical Representatives

The MAH/Manufacturers/LTR shall ensure that there is an appropriate pharmacovigilance and risk management systems in place to assure responsibility for their products on the market.
Local Technical Representatives (LTRs) in Rwanda operate pharmacovigilance activities under the supervision of QPPV of the MAH/Manufacturer. The LTR may be an employee of MAH or a person with adequate qualification appointed by the MAH among the personnel of the company or institution distributing the product.
They shall:

a) Continuously monitor pharmacovigilance data, the examination of options for risk minimization and prevention and that appropriate measures are taken by the marketing authorization holder,
b) Carry out scientific evaluation of all information and report safety concerns arising from use of the product within or outside the terms/jurisdiction of its marketing authorization,
c) Submit accurate and verifiable data on serious and non-serious adverse reactions to the Rwanda FDA within the legally required time-limits,
d) Ensure quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signals,
e) Ensure effective communication with Rwanda FDA including communication on new or changed risks, risk management systems, periodic safety update reports and the update of product information by the marketing authorization holder in the light of new scientific knowledge,
f) Ensure appropriate communication of relevant safety information to healthcare professionals and patients,
g) Appoint a qualified person responsible for pharmacovigilance (QPPV) who should be residing in at least one EAC Partner State,
h) Adequately support the QPPV and ensure that they have access to all resources relevant for the fulfilment of the QPPV's responsibilities and tasks,
i) Ensure the QPPV is trained and well equipped to perform assigned tasks,
j) Establish and maintain a system to collect, collate, and evaluate pharmacovigilance data,
k) establish documentation on the quality system which shall include in relation to their human resource management, job description, organizational chart and instructions on critical processes and records on pharmacovigilance system master file (PSMF),
l) Meet legal obligations for reporting of suspected adverse events and the preparation and the submission of periodic Safety Update Reports,
m) Report to Rwanda FDA any published suspected ADRs/events related to their medicines and health technologies, occurring in and outside Rwanda. 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 suspected medicine is usually the one stated as such in the body or title of the article by the author(s),

n) provide evidence to the Rwanda FDA/ PV-SM Division on compliance to sanctions or recommendations,

o) liaise with health care providers and public health institutions on updates on approved safety information and safety issues by Rwanda FDA/ PV-SM Division i.e Summary of Product Characteristics and Patient Information leaflet,

p) Continuously monitor pharmacovigilance data, the examination of options for risk minimization and prevention and that appropriate measures are taken by the marketing authorization holder,

q) Submit or communicate scientific evaluation of all information and report safety concerns arising from use of the product within or outside the terms/jurisdiction of its marketing authorization,

r) Implement feedback/regulatory action taken for safety reasons on medical products

3.2.6Qualified Person Responsible for Pharmacovigilance (QPPV)

The QPPV should be appropriately qualified, with documented experience in all aspects of pharmacovigilance in order to fulfill the responsibilities and tasks of the post.

A QPPV responsible for safety of medical products shall have a minimum of Bachelor of Pharmacy degree with appropriate training and knowledge in Pharmacovigilance, and recognized/ registered with Health professional bodies in any of the EAC Partner States.
In case of other health technologies, a QPPV shall have a minimum of Bachelor in Health Sciences with appropriate training and knowledge in Pharmacovigilance, and recognized/ registered with their relevant professional bodies.

The QPPV shall:

a) provide information to Rwanda FDA on all adverse events,
b) Ensure submission of safety reports to the Rwanda FDA,
c) Supervise the provision of ICSRs from countries outside Rwanda whenever applicable,
d) Ensure submission of the Periodic Safety Update Reports (PSURs)/Periodic Benefit Risk Evaluation Reports (PBRERs)/Development safety update reports (DSURs) reports to Rwanda FDA within the stipulated timelines,
e) Inform Rwanda FDA about any significant safety issue(s) or action(s) taken by relevant foreign Health Authorities, including the rationale for the action taken, have oversight of the safety profile of the medical product under her/his scope and be aware of the emerging safety concerns,
f) Have sufficient oversight of the content of risk management plans,
g) Be involved in the review and sign-off of protocols of post-authorization safety studies conducted within Rwanda or pursuant to a risk management plan agreed in the region,

h) Participate in post-authorization safety studies and provide results as requested by Rwanda FDA
i) Be involved in the design and approval process of post-authorization safety studies and provide results as requested by Rwanda FDA,
j) Ensure submission of all pharmacovigilance-related documents in accordance with the legal requirements and Good Pharmacovigilance Practices (GVP),
k) Ensure the necessary quality, including the correctness and completeness, of pharmacovigilance data submitted to Rwanda FDA,
l) Ensure a full and prompt response to any request from Rwanda FDA for the provision of additional information necessary for the benefit-risk evaluation of a medicinal product,
m) Provide input into the preparation of Regulatory action in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and communication to patients and healthcare professionals),
n) Act as a single pharmacovigilance contact point for Rwanda FDA.

3.2.7 Academia

Academia shall have following roles and responsibilities:

a) Develop and incorporate the Pharmacovigilance training modules in the curricula of health professionals,
b) Provide pre-service, in-service and continuous professional development trainings on Pharmacovigilance,
c) Participate actively in development of PV training materials,
d) Carry out safety studies related to medical products and health technologies,
e) Collaborate with Rwanda FDA, MAH and other relevant stakeholders in PV activities,
f) Sharing of safety information and study findings related to medical products and health technologies with Rwanda FDA.

3.2.8 Research Institutions

Research institutions including CROs shall have following roles and responsibilities:

a) Carry out safety studies related to medical products and health technologies,
b) Collaborate with Rwanda FDA, MAH and other relevant stakeholders in PV activities,
c) Sharing of safety information and study findings related to medical products and health technologies with Rwanda FDA.

3.2.9 Development Partners

Development partners in collaboration with the Ministry of Health, Regional economic blocks, Rwanda FDA and other stakeholders shall provide both financial and technical support during implementation of pharmacovigilance activities at all levels.

3.2.10 Ministry Responsible for Health

The Ministry of Health shall;

a) Develop and review policies and legal framework to strengthen pharmacovigilance activities,
b) ensure effective integration of pharmacovigilance activities within public health programs and health facilities,
c) Mobilize and provide resources for pharmacovigilance activities to health facilities and Rwanda FDA.

3.2.11East African Community Secretariat

a) The roles of EAC secretariat in the process of strengthening pharmacovigilance activities in the region will include and not limited to:
b) Overall co-ordination of joint EAC regional pharmacovigilance related activities,
c) Technical and financial resource mobilization to support implementation of the activities,
d) Coordinating and organizing technical capacity building sessions for the region,
e) Undertaking lead in advocacy sessions at regional policy levels and international community in line with pharmacovigilance systems strengthening,
f) guidance on the overall regional pharmaceutical policy framework and its implementation including pharmacovigilance system strengthening,
g) Coordination of communication on safety messages with regional and international stakeholders,
h) Organizing of regional public hearings for safety-related referral procedures
i) Coordination and monitoring of Post-authorization safety and efficacy studies in the region,
j) Coordinate regional development and drafting of any required SOPs and Tools in relation to implementation of Pharmacovigilance,
k) Sharing of safety information within the EAC partner states NMRAs.

3.2.12Patients, Health care providers and consumers

Patients, health care providers and consumers should report any suspected adverse reaction or event associated with the use of medical products and health technologies immediately to the nearest health facility, health care provider, MAH or directly to Rwanda FDA.

3.2.13Collaboration with Uppsala Monitoring Center (UMC)

Rwanda FDA shall collaborate with the WHO Collaborating Center for Safety Monitoring (UMC) in the following area:

a) Receive, share and store safety reports

b) Provide tools, trainings and access to information systems
c) Monitoring of Signals from global WHO database
d) Communicate signal analyses and clinical review of analyses by experts,
e) Develop and maintain WHO ADRs terminology and use of medical dictionary for regulatory activities.

CHAPTER 4: ADVERSE EVENTS REPORTING

4.1 SPONTANEOUS REPORTING

Submission of a report does not constitute an admission that the medical personnel or manufacturer or the product caused or contributed to the event. All reports submitted to Rwanda FDA shall be treated with utmost confidentiality to protect both the reporter and the patient. In addition, no reporter shall be penalized for reporting on the AEs including medication errors. It is important that any AE is reported even when not certain about the suspected medical product and health technology causing the same.

4.1.1Who should report AEs?

Everyone is encouraged to report adverse events through the reporting structure. Reporters from both public or private health sector are expected to submit reports to Rwanda FDA. These shall include medical doctors, dentists, pharmacists, clinical officers, pharmaceutical technologists, nurses, public health programs, staff in medical laboratories, community health workers, pharmaceutical manufacturing companies, marketing authorization holders (MAHs), importers, distributors, Patients or patient representatives/ guardians, researchers and principal investigators.

Reports from patients are a potentially valuable source of information and should receive appropriate attention. A simplified reporting form (Patient reporting form Annex 2) shall be used to collect information on adverse experience from patients. Patients are encouraged to report adverse events and seek medical attention through their health care providers. Further information on the report can be sought from the health care provider for serious and/or unknown reaction reported directly from patients. Patients who experienced serious adverse drug reaction should be given special cards (Patient ADR Alert Card Annex 5) by the health care provider who diagnosed and managed the reaction.

The card will alert all health care providers that the bearer of the card had experienced serious reaction(s) (e.g. hypersensitivity reactions) or had experienced a serious adverse reaction to a particular medicine. The card will be carried by the patient at all times and be presented to health care provider at the time of consultation. This will help the health care provider to identify the patient's medicines-related co-morbidity and prevent similar reactions.

4.1.2 What to report?

It is important to report the following:

a) All serious and non-serious adverse events/reactions related to the medical products and health technologies

b) All local expected and/or unexpected suspected adverse reactions and events to medicinal products, traditional/alternative/herbal medicines, biologicals, vaccines, x-ray contrast media, medical devices, diagnostics and cosmetics,
c) All Adverse Events Following Immunization (AEFI)
d) All medication errors,
e) All suspected AEs that may be associated with suspected or confirmed quality defects including substandard and/or falsified medical products,
f) Case reports of acute and chronic poisoning (toxicity),
g) Abuse, overdose, misuse and off label use of medical products,
h) Adverse interactions of medicines with chemicals, other medicines and food,
i) Lack of therapeutic efficacy/therapeutic failure,
j) Any AEs observed in pregnancy or during breastfeeding,
k) All SAEs and SUSARs on exposure to investigational products,
l) Other patient or community safety concerns about medical products,
m) All suspected poor-quality medical products
n) Periodic Safety Update Report (PSUR)/ Periodic Benefit/Risk Evaluation Report (PBRER)

4.1.3When to report?

Any suspected AE should be reported as soon as possible to Rwanda FDA via telephone, e-mail or in writing according to the following timelines:

4.1.3.1 Healthcare Professionals/Patients:

a) Fatal and other serious adverse events/adverse drug reaction be notified within 24 hours and a complete report shall be submitted by Healthcare Professional within 7 calendar days,
b) Non-serious adverse events/adverse drug reaction shall be reported within 7 calendar days

4.1.3.2 Marketing Authorization Holders:

a) Fatal and other serious adverse events/adverse drug reaction shall be notified as soon as possible but not later than 7 calendar days;
b) A complete report for fatal and other serious adverse events/adverse drug reaction that have occurred in Rwanda and in EAC region shall be reported within 15 calendar days.
c) Non-serious adverse events/adverse drug reaction local reports shall be submitted within 30 calendar days;
d) All foreign serious and non-serious adverse events/reactions to medical products registered in Rwanda shall be reported as per regular timelines within the Periodic Safety Update Report (PSUR)/ Periodic Benefit/Risk Evaluation Report (PBRER).

4.1.3.3 Timelines for providing feedback.

The timelines for providing feedback are the following:

a) Rwanda FDA shall acknowledge receipt of safety reports as soon as possible but not later than 7 days.
b) Rwanda FDA shall provide feedback within 30 calendar days

4.1.4 How and where to report?

All the filled AE reporting forms i.e. forms for reporting suspected adverse drug reactions/adverse event following immunizations, adverse event following use of a medical device and forms for reporting suspected poor quality product (Annex 1, Annex 3 and Annex 4 respectively) shall be sent to Rwanda FDA either electronically, via email: info@rwandafda.gov.rw or by post on Rwanda FDA, P.O.Box 84 Kigali, Rwanda . The occurrence of AEs can be communicated by telephone, fax or e-mail. The MAHs shall report via CIOMS 1 form-E2B -XML file via email or report directly by filling the relevant form on the Rwanda FDA website (**www.rwandafda.gov.rw**). Reports originating from clinical trials shall be reported via CIOMS form or trial specific forms. Reporting of safety information at various levels shall be as described in the flow of information (in section 2.6)

Rwanda FDA shall share safety reports to the EAC NMRAs and other collaborating institutions via the shared portal.

4.1.5 Basic Principles of efficient reporting

4.1.5.1 In-time reporting

The in-time reporting are as follows:

a) Report the suspected adverse events as soon as it occurs/as per section4.1.3.3
b) Send the report quickly to Rwanda FDA

4.1.5.2 Strong suspicion on both initial and follow up reports

The strong suspicion on both initial and follow up ofreports are:

a) Closely monitor for signs and symptoms that may enhance or exclude the possibility of a drug induced event,
b) All follow -up/supplementary information should be documented and submitted to Rwanda FDA with "FOLLOW UP REPORT" clearly indicated.
c) Make sure that the patient names and patient unique identifier numbers are the same on both initial and follow-up reports.
d) It is very important that follow-up reports are accurately identified and linked to the initial report.

4.1.6 Accuracy and completeness

Ensure that each suspected AEs reporting for misfiled in accurately and with all the necessary information, as much as is available to you. This is very important for assessing the causality of the medicines and health technology to have caused that event.

4.1.7 Information to be provided when reporting adverse events

4.1.7.1 Patient details

For Partner State cases, this includes the initials of the patient's name, age/date of birth, sex, weight, height, pregnancy status, in-patient/outpatient no., patient address, any known allergy, and the ward/clinic where the patient was seen. It is also important to fill in the name, address, location (county) and contacts of the institution to assist in contacting the patient for follow-up when necessary.

4.1.7.2 Details on the adverse reaction/event

A brief description of the reaction/event, date of onset, severity (e.g. mild, severe, fatal) action taken (e.g. drug withdrawn, dose reduced) outcome (whether the patient is recovering, recovered) and causality (e.g. certain, possible etc.) should be filled and checked on the form as appropriate.

4.1.7.3 Details on the suspected product

This includes the name (generic and brand), dose, route and frequency, date the medicine was started and stopped and the indication. It is very important to give details of any other medicines that the patient is on that may not be necessarily responsible for the reaction. The additional information required includes batch number, manufacture date and expiry date.

4.1.7.4 Details of the reporter

It is important to give contact details as a reporter in case of any clarification or any additional information about the report that may be required by Rwanda FDA. The reporter details include the name, email address, designation and phone number.

If the above information is missing, the report may not be useful. Remember to fill in all information accurately and in clear legible writing when using the manual forms.

4.2 ACTIVE SURVEILLANCE REPORTING

Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of

adverse events via a continuous pre-organized process. An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management program. For active surveillance reporting refer to Annex 11 of this guideline.

4.3 VIGILANCE OF HEALTH TECHNOLOGIES

Rwanda FDA recognizes that various PHPs will have reporting requirements that do not fit well with aforementioned requirements. Medical products and health technologies include but are not limited to vaccines, medical devices, herbal and traditional medicines, nutraceuticals, blood products, veterinary products and biopharmaceuticals. The minimal PV requirements are here with specified.

4.3.1 Adverse Events Following Immunization (AEFI)

Vaccine safety monitoring is a collaborative process that involves the National Vaccines and immunization Programs, Rwanda FDA, healthcare providers, consumers, Development partners and other stakeholders. The AEFIs shall be reported using the ADR/AEFI form (Annex 1).
AEFIs are grouped into five categories which includes; vaccine product related reaction, vaccine quality defect related reaction, immunization errors related reaction, immunization anxiety related reaction and coincidental event.

4.3.1.1 What AEFIs to report?

Health care providers and care givers should report any AEFI that is of concern. Both minor and serious AEFI cases should be reported.

This includes:

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 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 e.g. anaphylaxis, hives, bronchospasm, edema
e) Clusters of events (> 2 cases of same event in same month from the same facility) 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.

4.3.1.2 Conducting an AEFI investigation

Additional investigation on some AEFIs may be required to ascertain the underlying cause of the AEFI. The purpose of the investigation is to:

a) Confirm the reported diagnosis and timing of AEFI
b) identify details of vaccine(s) administered
c) determine the cause of AEFI
d) document the outcome of the reported adverse event
e) determine whether the reported event is a single incident or part of a cluster
f) identify and address the operational aspects of the immunization program which may have led to immunization errors

The AEFIs that require further investigation include:

a) Serious AEFIs
b) Clusters of minor AEFIs
c) occurrence of events above the expected rate or of unusual severity
d) signals and events associated with old or newly introduced vaccines
e) AEFI that may have been caused by immunization error (e.g. bacterial abscess, severe local reaction, high fever or sepsis, BCG lymphadenitis, toxic shock, clusters of AEFIs)
f) Significant events of unexplained cause occurring within 30 days after a vaccination (not listed in the product label), or;
g) Events causing significant parental or community concern.

The Pharmacovigilance Advisory Committee shall review all reported serious AEFI presented to them for expert opinion, carries out causality assessment, draws conclusions and makes recommendations to improve the immunization program and promote the safety of vaccines.

For comprehensive guidance on vaccine vigilance, cross refer to the; WHO global manual on surveillance of AEs following immunization and causality assessment of Adverse Event Following Immunization (AEFI) & user manual for the revised WHO classification (second edition)

4.3.2 Adverse events following the use of medical devices

An event/incident including a malfunction or deterioration in the characteristics or performancedue to a medical device is subject to be reported if it meets the following criteria:

- For IVDs (In-vitro diagnostics) where there is a risk that an erroneous result would either
  a) lead to a patient management decision resulting in an imminent life-threatening situation to the individual being tested, or to the individual's offspring, or

b) Cause death or severe disability to the individual or foetus being tested, or to the individual's offspring, all false positive or false negative test results shall be considered as events.

- For all other IVDs, false positive or false negative results falling outside the declared performance of the test shall be considered as events.
  a) Unexpected adverse reaction or unexpected side effect
  b) Interactions with other substances or products
  c) Degradation/destruction of the device (e.g. fire)
  d) Inappropriate therapy,
  e) An inaccuracy in the labelling, instructions for use and/or promotional materials. Inaccuracies include omissions and deficiencies. Omissions do not include the absence of information that should generally be known by the intended users.
  f) The medical device is considered to be the contributing cause of the incident

The incident caused or could have caused one of the following outcomes:

1) Death of patient, user or another person.
2) A serious deterioration in state of health of a patient, user or other person in the form of:
   a) life-threatening disease/illness
   b) Permanent damage, injury or impairment of a body function.
   c) necessary medical or surgical treatment to prevent life-threatening illness, permanent injury
   d) Any indirect harm caused by incorrect diagnostic or in Vitro Diagnostic Device (IVD) test results or caused by the use of in-vitro fertilization (IVF) / assisted reproductive technology (ART) equipment used in accordance with the manufacturer's instructions for use.
   e) Fetal death, fetal injury or congenital abnormalities

Any incident, whether the fault is due to technical faults or defects in the equipment, instruction manual, marking, use or maintenance of the equipment must be reported. Events due to the intervention of healthcare professionals regardless of the serious outcome must also be reported.

On identifying a significant increase or trend of events or incidents that are usually excluded from individual reporting, the manufacturer or the MAH must report to Rwanda FDA. The manufacturer should have suitable systems in place for proactive scrutiny of trends in complaints and incidents occurring with their devices. Field Safety Notices (FSN) and Field Safety Corrective Actions (FSCA) including those based on incidents occurring outside Rwanda must be reported to Rwanda FDA

The MAH may be requested by Rwanda FDA to conduct a concise critical analysis of the safety and performance of the medical device or IVD and submit results within a specified time frame. In addition, anybody can report incidents; however, healthcare professionals and manufacturers as

well as MAHs, distributors and importers of medical devices are obliged to report incidents. Moreover, manufacturers must report field safety corrective actions for marketed products.

The following timelines apply for the reporting of incidents that have occurred Rwanda:

a) Serious public health threat: immediately (without any delay that could not be justified) but not later than 24 hours after awareness of this threat.
b) Death or Unanticipated serious deterioration in state of health: immediately (without any delay that could not be justified) after the manufacturer has established a link between the device and the event but not later than 10 elapsed calendar days following the date of awareness of the event.
c) Others: Immediately (without any delay that could not be justified) after the manufacturer established a link between the device and the event but not later than 30 elapsed calendar days following the date of awareness of the event.

Conditions where reporting is not required include:

a) Deficiency of a device found by the user prior to its use
b) Adverse event caused by patient conditions
c) Service or shelf life of the medical device exceeded
d) Protection against a fault functioned correctly
e) Expected and foreseeable side effects
f) Negligible likelihood of occurrence of death or serious injury

The periodic summary reports should include the full details of vigilance issues, including the status of any Field Safety Corrective Actions or Notices. All adverse events related to medical devices should be reported to Rwanda FDA using the suspected adverse event/incidence reaction reporting form (Annex 3).

4.3.3 Adverse Events Due To Traditional/ Herbal Medicines

Adverse events (AEs), Case reports of acute and chronic poisoning (toxicity) and adverse interactions with other medical products and food related to herbal products shall be reported to the Rwanda FDA using the suspected AE reporting form (Annex 1). In addition, any other factors affecting product safety should also be reported using the form for reporting poor quality medicinal products (Annex 4).

4.3.4 Reporting of adverse events in clinical trials

The following apply to the reporting of adverse events of investigational products in clinical trials by investigators and sponsors:

1. A Fatal or life-threatening unexpected SAEs (local) shall be sent as a notification as soon as possible (within 24 hours) but no later than 7 days after first knowledge of reaction followed by complete report within the next 8 calendar days.

2. For all other serious non-fatal AEs shall be filed as soon as possible but not later than 15 calendar days.
3. Any frequent adverse event to the product shall receive immediate medical attention and reported to Rwanda FDA within7 calendar days.
4. Foreign NMRA decisions that affect the safety or use of the product under study shall be reported to NMRAs within 7 calendar days through a detailed report
5. Literature reports that affect the safety of the product under study shall be submitted within 15 days thorough a detailed report and a copy of the publication
6. The suspected unexpected serious adverse reactions (SUSARs) to be reported include those which occur within and outside the concerned trial.
7. Sponsors should ensure that processes are in place, before the trial starts, for expedited reporting of any SUSARs to Rwanda FDA
8. The investigator should ensure that all serious adverse events are reported promptly to the Rwanda FDA within timelines.

4.4 REPORTING OF SUSPECTED POOR QUALITY MEDICAL PRODUCTS

All healthcare providers in the private and public sector can alert Rwanda FDA on product quality issues. The poor-quality issues may include color change, separation of components, powdering, crumbling, caking, molding, change of odor, mislabeling, incomplete pack, suspected contamination, questionable stability, defective components, poor packaging/poor labelling, therapeutic failures and receiving expired medicines. This can be reported to Rwanda FDA using the form for reporting poor quality medical products and health technologies (Annex 4.)

CHAPTER 5: RISK MANAGEMENT SYSTEMS

Medical products and health technologies are authorized on the basis that in the specified indication (s), at the time of authorization, the risk-benefit balance is judged to be positive for the target population. Generally, medical products and health technologies will be associated with adverse reactions/events and these will vary in terms of severity, likelihood of occurrence, effect on individual patients and public health impact. However, not all adverse reactions/events and risks will have been identified at the time when an initial marketing authorization is granted and some will only be discovered and characterized in the post-authorization phase.

The aim of a risk management plan (RMP) is to document the risk management system considered necessary to identify, characterize and minimize medical products and health technologies important risks.

The medical products RMP shall contain:

a) the identification or characterization of the safety profile of the medical products and health technologies, 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) the planning of pharmacovigilance activities to characterize and quantify clinically relevant risks, and to identify new adverse reactions/events (the 'pharmacovigilance plan');
c) The planning and implementation of risk minimization measures, including the evaluation of the effectiveness of these activities (risk minimization plan).

5.1 GENERAL PRINCIPLES OF RISK MANAGEMENT

The MAH shall have RMP for their medical and health technologies throughout its life cycle. RMP shall be proportionate to the identified risks and the potential risks of the medical products and health technologies the need for post-authorization safety data.The RMP is a dynamic document that should 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.

The safety concerns in the RMP will be reduced on the following circumstances:

1. It may be that important potential risks can be removed from the safety specification in the RMP:
    a) when accumulating scientific and clinical data do not support the initial supposition, the impact to the individual has been shown to be less than anticipated resulting in the potential risk not being considered important, or when there is no reasonable expectation that any pharmacovigilance activity can further characterize the risk

b) they need to be reclassified to 'important identified risks' (e.g. if scientific and clinical data strengthen the association between the risk and the product).

2. In certain circumstances, where the risk is fully characterized and appropriately managed, important identified risks may be removed from the safety specification (e.g. for products marketed for a long time for which there are no outstanding additional pharmacovigilance activities and/or the risk minimization activities recommending specific clinical measures to address the risk have become fully integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines).
3. Given the overall aim of obtaining more information regarding the risk-benefit balance in certain populations excluded in the pre-authorization phase, it is expected that as the product matures, the classification as missing information might not be appropriate anymore once new data become available, or when there is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of the product with respect to the areas of missing information.

The overall aim of risk management is to ensure that the benefits of a particular medical products and health technologies exceed the risks by the greatest achievable margin. The primary aim and focus of the RMP remains that of appropriate risk management planning throughout a medicinal product's life cycle. 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. Applicants/marketing authorization holders shall be required to comply with legislation on risk management in Rwanda as well as international standards. Product information, medical treatment guidelines and any materials produced by marketing authorization holders or Rwanda FDA shall guide healthcare professionals and patients in management of both benefit and risks.

5.2 RISK MANAGEMENT PLAN FORMAT

The RMP consists of seven parts. The submitted RMP shall follow the format of table 1 as shown below. Part II of the RMP Safety specification is subdivided into sections, so the content can be tailored to the specifics of the medicinal product. This part generally follows the section titles in the safety specification of ICH E2E. The modular structure aims to facilitate the update of the RMP; in addition, in specific circumstances certain RMP sections may have reduced content requirements. However, the RMP document is expected to be submitted as one single document including all sections and annexes, as relevant.

Table 1 Overview of the RMP parts and sections

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 Rwanda FDA 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

The amount of information, particularly in RMP part II, should be proportionate to the identified risk and the potential risk, and will depend on the type of medicinal product, its risks, and where it is situated in its lifecycle.
It is recommended, where appropriate, that the RMP document includes all relevant medicinal products from the same applicant/marketing authorization holder containing the same active substance (s) (i.e. the RMP is an active substance-based document).

Information in the RMP should be provided in enough detail whilst avoiding unnecessary text that distracts from the key issues to be considered for risk management of the product. However, the safety specifications in the RMP should not be a duplication of data submitted elsewhere in the dossier, unless the sections are intended to be common sections with other documents such as the PSUR. Where applicable, the information in the RMP should 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. Any data included in the RMP should be consistent with other sections of the dossier. Links or references to relevant sections of the non-clinical and clinical overviews and summaries should be included in the RMP. For new RMP submissions for nationally authorized products with limited safety data in the dossier, the RMP may contain the relevant safety data and discussion.

To aid consistency between the information provided in the dossier and the RMP, table 2 below 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.

In the context of a centralized procedures, the RMP should be submitted as part of an eCTD submission; however, for non-centralized procedures the RMP submission might still be part of a CTD submission. eCTD data/submissions in this section should be read as eCTD or CTD data/submission, corresponding to the type of submission to Rwanda FDA.

Table 2: Mapping between RMP modules and information in eCTD

RMP	CTD
Part I Active substance information	Module 2.3 Quality overall summary Module 3Quality
Part II	
Module SI Epidemiology of the target population	Module 2.5 Clinical overview
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 (SPC)
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

Only key literature referenced in the RMP should be included in RMP (Annex 6). This should be in the format of electronic links or references if already included elsewhere in eCTD.

The description of the parts and sections of an RMP will provide guidance on the main topics to be addressed within each specific area. However, some sections may not be relevant to all medicinal products and there may be additional topics that need to be included but are not mentioned in this guidance.

The RMP is part of the scientific dossier of a product and as such should be scientifically based and should not include any element of a promotional nature. The preliminary section of the RMP should include the following administrative information about the RMP document:

a) data lock point of the current RMP;
b) sign off date and the version number of the RMP;
c) 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;
d) The evidence of oversight from the qualified person for pharmacovigilance (QPPV) is not needed for versions submitted for assessment.

The QPPV's actual signature or the evidence that the RMP was reviewed and approved by the QPPV should be included in the finalized approved version of the document; for eCTD submissions, this would be the RMP with the last eCTD sequence of the procedure (e.g. closing sequence). 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.

5.3 RISK MINIMIZATIONS MEASURES

Risk minimization measures are interventions intended to:

a) prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine or health technologies, reduce their severity or impact on the patient should adverse reactions occur.
b) plan and implement risk minimization measures and assessing their effectiveness are key elements of risk management. Risk minimization measures may consist of routine risk minimization or additional risk minimization measures. Safety concerns of a medicinal 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 will be necessary to manage the risk and/or improve the risk-benefit balance of a medicinal product.
c) facilitate informed decision-making to support risk minimization when prescribing, dispensing and/or using a medicinal product. While routine measures are applied to every medicinal

product additional risk minimization activities should only be introduced when they are deemed to be essential for the safe and effective use of the medicinal product and should be developed and provided by suitably qualified people.

Routine risk minimization activities shall include the following:

1. **Summary of product characteristics (SmPC) and patient Information leaflet(PIL)**
The SmPC and the PIL are important tools for risk minimization as they constitute a controlled and standardized format for informing healthcare professionals and patients about the medicinal product. They provide information on undesirable effects of medicinal product and specific clinical measures to address the risks as per the Rwanda FDA guidelines for registration of medical product.

2. **Pack size.**
Since every pack size is specifically authorized for a medicinal product, planning the number of "dosage units" within each pack and the range of pack sizes available should be considered in form of routine risk management activity.

3. **Legal status.**
Controlling the conditions under which a medicinal product may be made available can reduce the risks associated with its use or misuse.

The marketing authorization must include details of any conditions or restrictions imposed on the supply or the use of the medicinal product, including the conditions under which a medicinal product may be made available to patients. This is commonly referred to as the "legal status" of a medicinal product. This includes information on whether or not the medicinal product is subject to medical prescription. It should also restrict where the medicinal product can be administered (e.g.in a hospital) or by whom it should be prescribed (e.g. specialist).

For medicinal products only available on prescription, additional conditions should be imposed by classifying them into those available only upon either a restricted medical prescription, or upon a special medical prescription.

a) Restricted medical prescription

The following factors should be considered when classifying drug use as for restricted medical prescription:

i. The medicinal product, because of its pharmaceutical characteristics or novelty or in the interests of public health, is reserved for treatments which can only be followed in a hospital environment.
ii. The medicinal product is used in the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow-up may be carried out elsewhere.

iii. The medicinal product is intended for outpatients but its use may produce very serious adverse reactions requiring a prescription drawn up as required by a specialist and special supervision throughout the treatment.

b) Special medical prescription

For classification, as 'subject to special medical prescription', the following factors shall be taken into account:

i. The medicinal product contains, classified as a narcotic or a psychotropic substance within Rwanda regulations.
ii. the medicinal product is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes, or
iii. The medicinal product contains a substance which, by reason of its novelty or properties, could be considered to have potential for abuse.

Categorization in Rwanda FDA

a) There is the possibility of implementing sub-categories at Partner State level, which permits the Partner States to tailor the above-mentioned classifications to their national situation. Therefore,the definitions and implementation vary in those Partner States where the sub-categories exist.

b) The introduction of additional risk minimization should be considered as a "Programme" where specific tools, together with an implementation scheme and evaluation strategy are developed. The description of risk minimization measures, an integral part of the RMP, should therefore give appropriate consideration to the following points:

i. Rationale: When additional risk minimization measures are introduced a rationale should be provided for those additional measures;
ii. Objectives: Each proposed additional risk minimization measures should include defined objective(s) and a clear description of how and which safety concern is addressed with the proposed additional risk minimization measure(s);
iii. Description: This section of the RMP should describe the selected additional risk minimization measures, including tools that will be used and key elements of content;
iv. implementation: This section of the RMP should provide a detailed proposal for the implementation of additional risk minimization measures (e.g. setting and timing or frequency of intervention, details of the target audience, plan for the distribution of educational tools; how the action will be coordinated where more than one marketing authorization holder is involved);
v. Evaluation: This section of the RMP should provide a detailed plan with milestones for evaluating the effectiveness of additional risk minimization measures in process terms and in terms of overall health outcome measures (e.g. reduction of risk).

Additional risk minimization measures that may be considered in addition to the routine measures, includes:

Educational Programmes

a) The content of any educational material should be fully aligned with the currently approved product information for a medicinal product, such as the SmPC and patient Information leaflet (PIL), and should add rather than duplicate SmPC and PIL information.
b) The aim of an educational Programme is to improve the use of a medicine by positively influencing the actions of healthcare professionals and patients towards minimizing risk.
c) Any educational material should focus on actionable goals and should provide clear and concise messages describing actions to be taken in order to prevent and minimized selected safety concerns risks. The aim of an educational Programme is to improve the use of a medicine by positively influencing the actions of healthcare professionals and patients towards minimizing risk.
d) In an educational Programme, the tools can have several different target audiences, can address more than one safety concern and can be delivered using a combination of tools and media (e.g. paper, audio, video, web, in-person training).
e) Promotional elements, either direct or veiled (e.g. logos, product brand colours, suggestive images and pictures), should not be included and the focus of the educational material should be on the risk(s) related to the product and the management of those risk(s) requiring additional risk minimization.

Educational tools

a) The educational tool should have a clearly defined scope and should include unambiguous statement(s) regarding the important risk(s) of concern to be addressed with the proposed tool, the nature of such risk(s) and the specific steps to be taken by healthcare providers and/or patients in order to minimize those risks. Elements for inclusion in an educational tool shall provide:
    i. guidance on prescribing, including patient selection, testing and monitoring;
    ii. guidance on the management of such risks (to healthcare professionals and patients or care givers);
    iii. Guidance on how and where to report adverse reaction of special interest.
b) There are 2 categories of educational tools, those targeting;

Healthcare workers

The aim of any educational tool targeting a healthcare professional should be to deliver specific recommendation(s) on the use (what to do) and/or contraindication(s) (what not to do) and/or warnings (e.g. how to manage an adverse reactions) associated with the medicine and the specific

important risks needing additional risk minimization measures, including:

a. selection of patients;
b. treatment management such as dosage, testing and monitoring;
c. special administration procedures, or the dispensing of a medicinal product;
d. Details of information which needs to be given to patients.
e. The format of a particular tool should depend upon the message to be delivered e.g. brochure, poster, checklists

Patients and community

The aim of tools targeting patients and/or care givers should be to enhance their awareness of patients or their care givers on the early signs and symptoms of specific adverse reactions causing the need for additional risk minimization measures and on the best course of action to be taken should any of those sign or symptoms occur.
This could provide information on dosing, diagnostic procedures and patient alert cards.

Controlled access Programmes

A controlled access Programme consists of interventions seeking to control access to medical product beyond the level of control ensured by routine risk minimization measures, i.e. the legal status. Controlled access should only be considered as a tool for minimizing an important risk with significant public health or individual patient impact for a product with clearly demonstrated benefits but which would not otherwise be available without a Programme where patient access is contingent on fulfilling one or more requirements prior to a product being prescribed or dispensed in order to assure its safe use.Some of the requirements that need to be fulfilled before the product is prescribed and/or dispensed and/or used in a controlled access.

Programme include (they may be included individually or in combination) as follow:

a) Specific testing and/or examination of the patient to ensure compliance with strictly defined clinical criteria;
b) Prescriber, dispenser and/or patient documenting their receipt and understanding of information on the serious risk of the product;
c) Explicit procedures for systematic patient follow-up through enrolment in a specific data collection system e.g. patient registry;
d) Medicines made available for dispensing only by Pharmacies which are registered and approved to dispense the product.

On occasions, a requirement to test or to monitor a patient in a specific way can also be used as a controlled access tool. Measures should be put in place to ensure that monitoring takes place according to the SmPC where this is critical to risk-benefit balance of the product.

Other risk minimization measures includes controlled distribution system, pregnancy prevention

programs and direct health care professional communication.

5.4 EFFECTIVENESS OF RISK MINIMIZATION MEASURES

Evaluating the effectiveness of additional risk minimization measures is necessary to establish whether an intervention has been effective or not, and if not why not and which corrective actions are necessary. The evaluation should be performed for the additional risk minimization tools individually and for the risk minimization Programme as a whole. Effective evaluation should be conducted at the most appropriate time, accounting for time required for launch of interventions the risk minimization measures, the estimated use of the product by the healthcare system and other relevant circumstances.

Periodic review of the effectiveness of one or more specific tools or the overall Programme, as appropriate, should be also planned. Time points of particular relevance are as follows:

a) After initial implementation of a risk minimization Programme (e.g. within 12-18 months), in order to allow the possibility of amendments, should they be necessary;
b) In time for the evaluation of the renewal of a marketing authorization

Effective evaluation should address different aspects of the risk minimization, i.e. the process itself (i.e. to what extent the Programme has been implemented as planned), its impact on knowledge and behavioral changes in the target audience (i.e. the measure(s)affectingbehavioral change), and the outcome (i.e. to what extent the predefined objectives of risk minimization were met, in the short and long term).

To evaluate the effectiveness of additional risk minimization measures ,two categories of indicators should be considered:

a) Process indicators. These are necessary to gather evidence that the implementing steps of additional risk minimization measures have been successful. These process indicators should provide insight into what extent the programme has been executed as planned and whether the intended impacts on behavior have been observed. Depending on the nature of the interventions various process indicators can be identified for the assessment of their performance including reaching the target population, assessing clinical knowledge and assessing clinical actions.
b) Outcome indicators. They provide an overall measure of the level of risk control that has been achieved with any risk minimization measure in place. The ultimate measures of success of a risk minimization programme are the safety outcomes, i.e. the frequency and/or severity of adverse reactions in relation to patients' exposure to the medicine outside of an interventional study setting (i.e. non-interventional setting) and those safety outcomes should be the outcome indicator(s).
c) Such an evaluation should involve the comparison of epidemiologic measures of outcome frequency such as incidence rate or cumulative incidence of an adverse reaction, obtained, e.g. in the context of post-authorization safety studies.

In addition to assessing the effectiveness of risk minimization measures in managing safety concerns, it is also important to monitor if the risk minimization intervention may have had unintended (negative) consequences relevant to the public health question under consideration, either in the short and/or long term.

5.5 MEDICAL DEVICES RISKMANAGEMENT

There are risks associated with every medical device and other health technologies that are on the market or during development. Manufacturers shall manage risks of their product throughout the entire lifecycle to monitor whether the risks continue to remain acceptable and whether any new hazards or risks of illness or injury associated with the use of the device for its intended uses and conditions of use are discovered. The risk management procedures shall be directly linked to the manufacturer's post-marketing surveillance procedures and shall focus on controlling and mitigating risks. Details on risk management activities shall be as described in the current ISO 14971:2007guidelines.

Manufacturers shall plan and perform internal quality audits to verify whether risk management activities and related results comply with planned and established procedures. The internal audits should ensure the continued effectiveness of the risk management system. Risk management activities should begin as early as possible in the design and development phase, when it is easier to prevent problems.

If at any time, a risk is determined to be unacceptable, the existing risk analysis should be re-examined and appropriate action taken to meet the risk acceptability criteria. If a new hazard is identified, four phases of risk management shall be performed.

After release of the device to market, risk management activities should be linked to quality management processes, for example, production and process controls, corrective and preventive actions (CAPA), servicing and customer feedback.

5.5.1 Risk management plan

Risk management planning shall be in the span of the entire lifecycle of a device. The plan shall include the following:

a) Scope of the plan, device and the life cycle phases
b) Design development process
c) Risk management activities and methods
d) Verification plan for risk control measures
e) Reviews
f) Allocation of responsibilities
g) Criteria for risk acceptability

The following risk management activities shall be included the plan as below:

a) Establishment of risk acceptability criteria
b) Risk analysis
c) Hazard Identification
d) Risk analysis methods

The following tools shall be considered for analysis and validation risk management;

a) Preliminary Hazards Analysis (PHA)
b) Fault Tree Analysis (FTA)
c) Failure Mode Effect Analysis (FMEA)
d) Failure Mode Effect and Criticality Analysis (FMECA)
e) Hazard and Operability Study (HAZOP)
f) Hazard Analysis and Critical Control Point (HACCP)
g) Risk evaluation including; Risk benefit analysis, Assessment of risks and Assessment of benefits.
h) Risk control and monitoring

Risk control activities may begin as early as design input and continue through the design and development process, manufacturing, distribution, installation, servicing and throughout the medical device life cycle.

Risk control measures may be examined in the following order:

a) inherent safety by design;
b) Protective measures in the device or its manufacture;
c) Information for safety, such as warnings, etc.
d) Overall risk evaluation

5.5.2 User-related hazards risk management

a) Manufacturer shall undertake efforts to control user-related hazards. The goal is to minimize use-related hazards, assure that intended users are able to use medical devices safely and effectively throughout the product life cycle. Risk Management will help to identify, understand, control and prevent failures that can result in-hazards when people use medical devices.
b) The following hazards typically should be considered in risk analysis: chemical hazards (e.g., toxic chemicals), Mechanical hazard (e.g., kinetic or potential energy from a moving object), thermal hazards (e.g., high temperature components), and electrical hazards (e.g., electrical shock, electromagnetic interference (EMI), and radiation hazards (e.g. ionizing and non-ionizing) and biological hazards (e.g., allergic reactions, bio-incompatibility and infections).
c) Thorough consideration of use-related hazards in risk management processes shall include the following tasks:

(a) identify and describe use-related hazards through analysis of existing information

(b) Apply empirical approaches using representative device users, to identify and describe hazards that do not lend themselves to identification or understanding through analytic approaches,
(c) Estimate the risk of each use-related hazard scenario.
(d) Develop strategies and controls to reduce the likelihood or mitigate the consequences of use-related hazard scenarios.
(e) Select and implement control strategies.
(f) Ensure that controls are appropriate and effective in reducing risk,
(g) Determine if new hazards have been introduced as a result of implementing control strategies,
(h) Verify that functional and operational requirements are met, and
(i) Validate safe and effective device use.

Human factors shall be considered in user device risk management. Human Factors engineering considerations and approaches should be incorporated into the design and risk management processes/activities in the following essential steps:

(a) Identify anticipated (derived analytically) and unanticipated (derived empirically) user related hazards.
(b) Describe how hazardous use scenarios occur (Prioritize and assess risks of use-related hazards).
(c) Develop, mitigate and verify strategies to control use-related hazards often require a combination of mitigation and control strategies.

Strategies to control or mitigate risks of use-related hazards shall include but not limited to the following:

(a) Modify device design to remove hazard or reduce its consequences:
(b) Make user interface, including operating logic, error tolerant (safety features):
(c) Alert users to the hazard.
(d) Develop written procedures and training for safe operation.
(e) Determine if the risks related to device use are acceptable and determine if new hazards have been introduced.
(f) Demonstrate safe and effective device use(validation).

5.5.3 Documentation of Risk management activities

Design and development activities targeted at controlling risks shall be supported by documentation. Documents or records resulting from risk management activities such as risk management procedures, reports, 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.

5.5.4 Traceability

Risk management data shall be utilized to define which devices, components, materials and work environment conditions require traceability. Risk management activities shall be used to establish criteria for traceability. Points to be considered include:

(a) Origin of components and materials;
(b) Processing history;
(c) Distribution and location of the device after delivery (to the first consignee);
(d) intended use of the device (i.e., life sustaining, life supporting, or implantable);
(e) Probability of failure;
(f) Need for safety related updates (i.e. recalls, advisory notices, field updates, etc.);
(g) Consequence of the failure for patients, users or other persons.

The records required for traceability shall consider all those devices, components, materials and work environment conditions, which could cause the medical device not to satisfy its specified requirements including its safety requirements.

5.6 CO-ORDINATION AND HARMONIZATION

If several products have the same active ingredient registered with Rwanda FDA, there should be a consistent approach in the use of additional risk minimization measures coordinated by Authority. In case of medical products of the same active ingredients are registered in at least 3 or more of the EAC Partner States, there should be a harmonized risk minimization measure that be instituted and coordinated by the EAC secretariat and the lead NMRA.

CHAPTER 6: POST-AUTHORIZATION SAFETY STUDIES

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

A PASS may be interventional or non-interventional. These guidelines will be for both interventional and non-interventional PASS, with a main focus on non-interventional studies , if a PASS is interventional Rwanda FDA guidelines for registration of clinical trials shall be followed

6.1 GENERAL REQUIREMENTS

Rwanda FDA shall require MAHs to conduct post-authorization studies on safety and efficacy as a condition at time of the granting of the marketing authorization or later as and when required. 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). A marketing authorization may be granted subject to the conduct of a PASS. The need for a PASS could be identified by Rwanda FDA during a post authorization procedure, for example, an extension or a variation to a marketing authorization, a renewal procedure or a PSUR procedure. 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 section (Chapter 5 (RMP) of these guidelines 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.

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 products,

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 a risk management measures.

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

6.2 APPLICATION PROCEDURE FOR PASS

Safety studies to be conducted within Rwanda, application shall be done according to the existing laws and regulations governing clinical research conduct in that country.
The application form to be used and registration procedures shall be as described in the applicable guidelines for registration of clinical trials. The MAH shall be required to state in the application form that the study is PASS and provide justification as to why it is not a clinical trial.

i. The MAH shall be required to submit to Rwanda FDA the PASS study protocol for review and approval. The study protocol should be developed by individuals with appropriate scientific background and experience. Guidance for the format and content of the protocol of non-interventional post authorization safety studies shall be as prescribed in Annex 7 of these guidelines.

ii. The qualified person responsible for pharmacovigilance (QPPV) or his/her delegate should be involved in the review and sign-off of study protocols required in the risk management plan to ensure compliance of the marketing authorization holder with its pharmacovigilance obligations.

iii. An overview of study designs and databases frequently used in post-authorization Safety studies has been provided in Annex 7.

iv. Information on studies conducted pursuant to an obligation imposed by Rwanda FDA shall be included in the risk management plan.

v. Non-interventional PASS shall be registered in Rwanda FDA clinical trials registry or recognized clinical trials registry before the study commences or at the earliest possible date, for example if data collection had already started for a study included

in the risk management plan.

vi. Pre-submission meetings might be requested from Rwanda FDA in order to clarify specific aspects of the requested study and to facilitate the development of the protocol in accordance with the objectives.

vii. Rwanda FDA 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;

6.3. STUDY CONDUCT

The study shall commence only when the written authorization from Rwanda FDA has been issued.
Non-interventional PASS shall be initiated, managed or financed by a marketing authorization holder voluntarily or pursuant to imposed obligations by Rwanda FDA
The marketing authorization holder shall ensure the fulfillment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified.
The conduct of the study shall follow Rwanda FDA guidelines for Good Clinical Practice (GCP), ethical considerations for conducting biomedical research and clinical trials to ensure the protection of the well-being and rights of participants in the study.
Additionally, 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.

The marketing authorization holder should ensure that the investigators are qualified by education, training and experience to perform their tasks.
Agreements between the marketing authorization holder and the investigators shall follow Rwanda FDA contractual requirements.

Non-interventional post-authorization safety 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. Payments to healthcare professionals for participating shall be restricted to compensation for time and expenses incurred.

6.4 SUBMISSION OF STUDY REPORTS

Biannual (every 6 months after commencement of study) progress reports on PASS studies shall be submitted to Rwanda FDA whether it was a requirement or conducted voluntarily.
If need arises, the Rwanda FDA might request progress report (ad hoc) 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 Rwanda FDA procedures or important safety communication about the product.
The progress report shall include relevant information to document the progress of the study, such as the number of patients who have been enrolled in to 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.

An interim report submitted shall include study results of any planned interim analysis of study data before or after the end of data collection.

Final study report including a public abstract shall be submitted to Rwanda FDA 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 7 and Annex 8) of these guidelines.

6.5 REPORTING OF SAFETY AND RISK-BENEFIT BALANCE DATA

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.
Any new information that may affect the risk-benefit balance of the product shall be communicated immediately within 14 calendar days in writing as an emerging safety issue to Rwanda FDA. The reporting shall be as per expedited reporting requirements described in section (reporting of event) of these guidelines.

Information affecting the risk-benefit balance of the medical products and health technology may include an analysis of adverse reactions and aggregated data.
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 section (chapter 7).

Individual cases of suspected adverse reactions and Serious Adverse Events that arise from the

studies shall be reported to Rwanda FDA according to the requirements set out in as stipulated in the applicable guidelines for registration of clinical trials and section (chapter 4).
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.

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.

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.
The Authority shall recruit a risk assessment technical expert committee to assess the risk-benefit balance,
If technical expertise not available in the country, it can contract another committee available in a different country. The role of the regulator to conduct risk benefit assessment on receipt of safety information following the conduct of a PASS not indicated and if the regulator does not have the capacity, the EAC can have the mandate to perform the role.

6.6 AMENDMENTS TO THE STUDY PROTOCOL

The study protocol shall be amended and updated as needed throughout the course of the study.
Any substantial amendments to the protocol after the study started shall be documented in the protocol in a traceable and auditable way including the dates of the changes.
If changes to the protocol lead to the study being considered an interventional clinical trial, Rwanda FDA shall be informed immediately and approval shall be obtained.
Application for amendment shall be as prescribed in Rwanda FDA regulations and guidelines for registration of clinical trials.

6.7 JOINT POST AUTHORIZATION STUDIES CONDUCTED IN THE EAC

MAH may apply for joint assessment of PASS if the study is to be conducted in EAC Partners states. The Application with protocols shall be submitted to the lead country as per EAC procedures.

The EAC secretariat shall organize a joint assessment meeting. The EAC shall communicate the recommendation to MAH on behalf of NMRAs. Recommendations from EAC shall be applied to register the PASS at each Partner State.

The assessors shall include the PV experts in the EAC expert working group from all the 7 NMRAs with additional experts on case by case basis.
If safety concerns apply to more than one medicinal product, the NMRAs following consultation

with the EAC advisory committee may encourage the marketing authorization holders concerned to conduct a joint PASS.

Requests to the marketing authorization holders shall contain the justification for the request of a joint study and may include core elements for the study protocol.
The lead NMRA shall support interactions between the concerned marketing authorization holders and providing suggestions for the joint study proposal.
The EAC shall established electronic study register for registration, transparency and sharing of information on PASS being conducted within the region.

The marketing authorization holders shall be required to register the approved PASS in the EAC PASS register and obtain EAC PASS registration number before the study commences or at the earliest possible date, for example if data collection had already started for a study included in the risk management plan.

The marketing authorization holders shall also enter in the EAC PASS Register all non-interventional PASS required in the risk management plan agreed in the EAC or conducted voluntarily in the EAC region.
Other requirements such as reporting of safety data shall be as described in previous sections in this chapter.

6.8 OUTCOME OF THE PASS APPLICATION

After the application has been reviewed by Rwanda FDA and the technical committees the following decisions shall be made within 60 working days.
Endorsement of the protocol. In case of endorsement, the assessment report may still include recommendations for amendments to the protocol. These recommendations are for consideration by the MAH and do not require resubmission of the protocol.
Objection to the protocol; In case of objection, resubmission of an amended protocol for reassessment will be required.

6.9 DATA MANAGEMENT AND PUBLICATION OF STUDY RESULTS

6.9.1 Data protection

a) Rwanda FDA rules and regulations regarding data transfer and publication shall be followed.

b) For non-interventional PASS imposed as an obligation, the MAH shall ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information and shall ensure that the confidentiality of the records of the study subjects remains protected.

6.9.2 Publication

a) 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.

b) 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.

6.9.3 Manuscript submission

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

6.10 QUALITY SYSTEMS, AUDITS AND INSPECTIONS OF PASS

a) The MAH shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified.

b) For PASS imposed as an obligation, the MAH shall ensure that the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

c) For PASS required in the risk management plan agreed in the EAC or conducted voluntarily in the EAC, record management and data retention shall follow Rwanda FDA and regional regulatory provisions.

6.11 CHANGES FOLLOWING RESULTS FROM A NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY

TheMAH shall evaluate whether the study results have an impact on the marketing authorization and shall, if necessary, submit to Rwanda FDA an application to vary the marketing authorization. The applications shall be as described in Rwanda FDA guidelines on variation for registered products. Following the review of the final study report, Rwanda FDA may recommend variation, suspension or revocation of the marketing authorization according to the provisions of laws and regulations.

6.12 IMPACT ON THE RISK MANAGEMENT SYSTEM

Information on non-interventional PASS conducted pursuant to an obligation imposed by Rwanda FDA or required in the risk management plan shall be included in the risk management plan as described in these guidelines.

i. Pharmaco-epidemiological studies may be performed using a variety of data sources. Traditionally, field studies were required for retrieving the necessary data on exposure, outcomes, potential confounders and other variables, through interview of appropriate subjects (e.g. patients, relatives) or by consulting the paper-based medical records.

ii. The advent of automated healthcare databases has remarkably increased the efficiency of pharmaco-epidemiological research. Generally, there are two main types of automated databases: those that contain comprehensive medical information, including prescriptions, diagnosis, referral letters and discharge reports, and those mainly created for administrative purposes, which require a record-linkage between pharmacy claims and medical claims databases. Depending on the outcome of interest, the validation may require either a case-by-case approach or just the review of a random sample of cases. Other key aspects may require validation where appropriate. There are many databases in place for potential use in pharmaco-epidemiological studies or in their validation phase.

iii. Marketing authorization holders should select the best data source according to validity (e.g. completeness of relevant information, possibility of outcome validation) and efficiency criteria (e.g. time span to provide results).

iv. Data sources that are selected, shall ensure both internal and external validity

v. With any data source used, the privacy and confidentiality regulations that apply to personal data should be adhered to.

CHAPTER7: SAFETY AND VIGILANCE PERIODIC UPDATE REPORTS

Periodic safety update reports (PSURS), periodic benefit-risk evaluation reports (PBRERS) & development safety update reports (DSURS) shall be submitted to Rwanda FDA on regular basis.

PSURs and PBRERs are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medical product for submission by marketing authorization holders at defined time points during the post-authorization phase.

There is a need for continuous and prompt analysis of safety, efficacy, and effectiveness information throughout the lifecycle of a medical product, as important findings occur and periodically to allow an overall assessment of the accumulating data. This is due to the fact that during approval, demonstration of safety and efficacy are generally based on data from a limited number of patients, many studied under the controlled conditions of randomized trials. Although the majority of new information will be safety-related, new information about effectiveness, limitations of use, alternative treatments, and many other aspects of the drug's place in therapy may be pertinent to its benefit-risk assessment.

PSUR provides a comprehensive picture of the safety of approved medicinal products, however assessment of the risk of a medicinal product is most meaningful when considered in light of its benefits and therefore PBRERs provides greater emphasis on benefit than the PSUR, particularly when the changes in the risk estimates is important. PBRER has therefore been extended to include benefits as well as safety and also provides greater emphasis on the cumulative knowledge regarding a medicinal product, while retaining a focus on new information.
The scope, objectives, format and content of the PSUR in Rwanda are based on those for the PBRER described in the current ICHE2C guideline. The PBRER format replaces the PSUR format previously described in the ICH-E2C(R1).

It is recognized that a concise discussion of benefit will usually be sufficient, unless the safety or benefit-risk profile has changed significantly during the reporting interval. Thus, the level of detail provided in certain sections of the PBRER (e.g., evaluation of safety and efficacy data, evaluation of safety signals, and benefit-risk evaluation) should be proportional to the medicinal product's known or emerging important risks and to evidence of emerging important benefits.
The main objective of PBRERs/PSURs is to present a comprehensive, concise, and critical analysis of new or emerging information on the risks of the medicinal product, and on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile.

7.1 SCOPE OF PBRERS/PSURS

The main focus of each PBRERs/PSURs shall be the evaluation of relevant new safety information

from the available data sources, placed within the context of any pertinent efficacy/ effectiveness information that may have become available since the international birth date (IBD),the date of the first marketing approval in any country in the world, or the development international birth date (DIBD), the date of first authorization for the conduct of an interventional clinical trial in any new safety and efficacy/effectiveness information discovered during the reporting be discussed in the appropriate sections of the PBRERs/PSURs.

7.2 GENERAL PRINCIPLES

7.2.1 PBRER for one active substance product

The PBRER should provide information on all approved indications, dosage forms, and regimens for the active substance, with a single Data Lock Point (DLP). In some circumstances, it will be appropriate to present data by indication, dosage form, dosing regimen, or population (e.g., children vs. adults) within the relevant section(s) of the PBRER. In exceptional cases, submission of separate PBRERs might be appropriate, for example, an active substance used in two formulations for systemic and topical administration in entirely different indications. In these cases, Rwanda FDA should be notified and their agreement obtained, preferably at the time of approval.

7.2.2 PBRERs for fixed dose combination product

For combinations of substances also marketed individually, information for the fixed dose combination may 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.

7.2.3 PBERs for Products manufactured and/or marketed by more than one company

Each MAH is responsible for submitting PBRERs for its own products. When companies are involved in contractual relationships (e.g., licensor-licensee), respective responsibilities for preparation and submission of the PBRER to Rwanda FDA should be clearly specified in a 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 should be included and discussed in the PBRER.
Standard for periodic benefit-risk evaluation reporting on marketed products (including approved drugs that are under further study) in Rwanda and in the EAC region shall follow current ICH guidelines Periodic Benefit-Risk Evaluation Report (PBRER)E2C.

7.3 FORMAT AND CONTENT OF PBRERS/PSURS

The format, presentation and content of PBRER and an outline of points to be considered in its preparation and submission shall follow current ICH guidelines Periodic Benefit-Risk Evaluation Report (PBRER) E2C.

7.3.1 The PBERS/PSURS shall contain at a minimum the following;

a) 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;
b) A scientific evaluation of the risk-benefit balance of the medicinal product;
c) 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;
d) Collection of adverse drug reaction (ADR) information (i.e. serious ADRs, non-serious ADRs, case reports published on international or local literatures including academic conferences)";
e) A comprehensive, concise, and critical analysis of product's known or emerging important risks and to evidence of emerging important benefits;
f) Summary of relevant new safety information that could have an impact on the benefit-risk profile of the product;
g) Summary of any important new efficacy/effectiveness information that has become available during the reporting interval;
h) 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;
i) Conducting an integrated benefit-risk evaluation for approved indications in case a new safety information that has emerged;
j) Recommend action(s) to optimize the benefit-risk profile.

7.3.2 Timelines for submission of PBERs/PSURs to Rwanda FDA

The Timelines for submission of PBERs/PSURs to Rwanda FDA shall be done as follows:

a) Foreign NMRA decisions that affect the safety or use of products marketed, donated, imported, and/or for compassionate use in Rwanda shall be reported to Rwanda FDA within 7 calendar days through a detailed report on the same.
b) It is the responsibility of the QPPV to ensure that PSURs are submitted according to this guideline.
c) The PSURs must be prepared by the MAH at the following intervals:
   i. immediately upon request
   ii. every 6 months from authorization until the product is placed in the market
   iii. every 6 months for the first two years on the market

iv. annually for the next two years
v. thereafter every 3 years

d) The following timelines apply for the submission of PSURs:
   i. within 70 calendar days of the DLP (Day 0) for PSURs covering intervals up 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 should be submitted upon request within 90 calendar days of the DLP, unless otherwise specified
e) The PSURs should emphasize on the following:
   i. Scientific evaluation of the benefit-risk profile
   ii. Summaries of relevant scientific/clinical data including literature searches.

The reaction terms used shall be in accordance with the Medical Dictionary for Regulatory Activities (MedDRA)terminology.

7.3.3 Criteria for inclusion of the signal in the PBER/PSUR

The following criteria for inclusion of the signal in the PBER/PSUR shall be considered:

i. If a PSUR is due to be submitted within 6 months of the completion, by the marketing authorization holder, the submission of a separate standalone signal notification is not required. If the data-lock point of the PBER/PSUR has elapsed by the time the marketing authorization holder has completed their assessment of the signal, it should be mentioned in the PBER/PSUR section 'Late breaking information' together with a proposal for further management of the signal.
ii. Regardless of their source, all validated signals and emerging safety issues for which the evaluation was concluded during the reporting interval of a PBER/ PSUR, or are ongoing at the time of a PBER/PSUR data lock point, should be reported in that PBER/PSUR.

7.4 DEVELOPMENT SAFETY UPDATE REPORTS (DSURS)

a) The Development Safety Update Report (DSUR) is a common standard for periodic reporting on medical products under development (including marketed medical products that are under further study).
b) The main focus of the DSUR shall be the data and findings from interventional clinical trials. Because clinical development of a drug frequently continues following marketing approval, relevant information from post-marketing studies shall also be included in the DSUR. DSUR shall concentrate primarily on the investigational product, providing information on comparators only where relevant to the safety of trial subjects.
c) The format, presentation and content of DSUR and an outline of points to be considered in its preparation and submission timelines shall follow current ICH guidelines E2F on Development Safety Update Report.

d) The DSUR should provide safety information from all ongoing clinical trials and other studies that the sponsor is conducting or has completed during the review period including:
   - Clinical trials using an investigational product (i.e., human pharmacology, therapeutic exploratory and therapeutic confirmatory trials [Phase I – III]);
   - Clinical trials conducted using marketed medical products in approved indications (i.e., therapeutic use trials (Phase IV);
   - Therapeutic use of an investigational products;
   - Clinical trials conducted to support changes in the manufacturing process of medicinal products;
   - Any significant other findings pertinent to the safety of the investigational products.

Sponsors and Marketing Authorization Holders shall be required to submit annual DSURs of their products to Rwanda FDA.

For products that are jointly registered in EAC, the MAH and sponsors shall be required to submit the PSURs/PBRERs/DSURs to the EAC web-based portal.

CHAPTER 8: CAUSALITY ASSESSMENT & SIGNAL MANAGEMENT

The collected adverse events should be systematically assessed to determine whether they are possibly related to the studied (or supplied) medical products in line with ICH-E2D.Rwanda FDA adopted to use the WHO Causality Assessment methods. For vaccines, causality assessment shall follow WHO User manual for causality assessment of AEFI.

A signal is any information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action. New aspects of a known association may include changes in the frequency, distribution (e.g. gender, age and country), duration, severity or outcome of the adverse reaction. A signal often relates to all medicinal products containing the same active substance, including combination products. Certain signals may only be relevant for a particular medicinal product or in a specific indication, strength, pharmaceutical form or route of administration where some signals may apply to a whole class of medicinal products.

Signal management is a set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, scientific literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed, as well as any related recommendations, decisions, communications and tracking. Management of signals is a requirement for marketing authorization holders, Rwanda FDA and Pharmacovigilance Advisory Committee (PAC).

8.1 SIGNAL MANAGEMENT

Signals can arise from a wide variety of data sources. Common sources for signals include spontaneous reporting systems, active surveillance systems, studies and the scientific literature reports. The process of signal management involves the following:

a) Signal detection
b) Signal evaluation and validation
c) Signal prioritization
d) Signal communication

These principles shall apply also for signal management of medical devices and other health technologies.

8.1.1 Signal detection

Signal detection is the process of looking for and/or identifying signals using data from any source.Signal detection should follow a methodology which takes into account the nature of data and the characteristics (e.g. time on market, patient exposure, target population) as well as the type of medicinal product concerned e.g. vaccines may require specific methodological strategies. Data from all appropriate sources should be considered. Clinical judgment should always be applied.

Signal detection may involve a review of ICSRs, statistical analyses, or a combination of both, depending on the size of the data set. When it is not relevant or feasible to assess each individual case (e.g. signals detected from published studies, healthcare record data), assessment of aggregated data should be considered.

Signal detection is often based on the periodic monitoring of databases of suspected adverse reactions, which can vary in size, e.g. marketing authorization holder databases, national databases, the database of the WHO Programme for international Drug Monitoring (VigiBase)

Signal detection is done by either the qualitative or quantitative method as follows:

a) Review of individual case safety reports (Qualitative methods). This is based on clinical evaluation by a Research Fellow who reviews data reported by the health worker for a single case or series of cases.
b) Statistical analyses in large databases /data mining (Quantitative). This technique analyses large volume data.

Further guidance on statistical aspects of signal detection are found in (Annex 9) of these guidelines.

8.1.2 Signal evaluation and validation

The process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal. This evaluation should take into account the strength of the evidence, the clinical relevance and the previous awareness of the association. The extent of evaluation performed during signal validation versus further assessment may vary according to Rwanda FDA procedures.
The following elements should be considered when performing signal validation based on the review of ICSR data:

a) Previous awareness such as whether the information was included in SmPC and PIL or whether the information has been assessed in RMP, PSUR and other Rwanda FDA procedure.
b) Strength of the evidence, taking into account the total number of cases (after exclusion of duplicates), number of cases in context of patient exposure, additional cases reported with related terms consistency of the evidence across cases, quality of the data and their

documentation, cases matching internationally agreed case definitions if applicable, dose-reaction relationship, possible mechanism based on a biological and pharmacological plausibility and disproportionality of reporting, if applicable,

Clinical relevance and context such as seriousness and severity of the reaction, outcome and reversibility of the reaction, additional insight on a known adverse reaction, e.g. in terms of its severity, duration, outcome, incidence or management, reactions occurring in the context of drug-drug interactions, reactions occurring in vulnerable populations, patients with pre-existing risk factors and other reactions such as overdose, abuse, misuse, off-label use, medication errors, and falsified products.

Additional sources of information may provide further evidence for or against a causal association, or a new aspect of a known association, and may be considered during further assessment of the signal, depending on their relevance for the signal and availability to the Authority. These may include:

a) clinical trial data;
b) findings regarding similar cases in the scientific literature, including information on substances of the same class of medicinal products;
c) information on the epidemiology of the adverse reaction or the underlying disease;
d) experimental and/or non-clinical findings;
e) databases with larger datasets, when the signal was detected from national or marketing authorization holder-specific databases;
f) healthcare databases that may provide information on characteristics of exposed patients and medicines utilization patterns;
g) Information from other NMRA authorities worldwide and expert opinion.

A validated signal can be further evaluated by taking into account all available evidence, to determine whether there are new risks causally associated with the active substance or medicinal product or whether known risks have changed. This review may include non-clinical and clinical data and should be as comprehensive as possible regarding the sources of information.

8.1.3 Signal prioritization

Signal prioritization aims to identify those signals suggesting risks with a potential important patients' or public health impact or which may significantly affect the risk-benefit balance of the medicinal product and thus require urgent attention and management without delay. Prioritization should be continuously performed throughout signal management process. The following should be considered when evaluating patients or public health impact:

a) the severity, seriousness, outcome and reversibility of the adverse reaction and the potential for prevention;

b) the patient exposure and the estimated frequency of the adverse reaction;
c) the patient exposure in vulnerable populations and/or in populations with different patterns of use, where appropriate;
d) the consequences of treatment discontinuation on the disease under treatment and the availability of other therapeutic options;
e) the expected extent of Rwanda FDA intervention (e.g. addition of adverse reactions, warnings, contraindications, additional risk minimization measures, suspension, revocation);
f) Whether the signal is likely to apply to other substances of the same class of medical product in some circumstances, signals that could cause media attention and/or public concerns (e.g. adverse events following mass immunization) may deserve special attention.

8.1.4 Signal validation and communication in Rwanda

Rwanda FDA shall validate and prioritize signals detected or that have been brought to its attention from any source, including EAC database. Rwanda FDA shall be responsible for updating the Rwanda PV data base.

8.2 EMERGING SAFETY ISSUES

This is a safety issue considered by a marketing authorization holder to require urgent attention by Rwanda FDA because of the potential major impact on the risk-benefit balance of the medicinal product and/ or on patients' or public health, and the potential need for prompt Regulatory action and communication to patients and healthcare professionals.

This includes:

a) Major safety issues identified in the context of ongoing or newly completed studies, e.g. an unexpectedly increased rate of fatal or life-threatening adverse events;
b) Major safety issues identified through spontaneous reporting or published in the scientific literature, which may lead to considering a contra-indication, a restriction of use of the medical product or its withdrawal from the market;
c) Major safety-related Regulatory actions outside Rwanda, e.g. a restriction of the use of the medical product or its suspension.

When the marketing authorization holder in Rwanda becomes aware of an emerging safety issue from any source, they should notify it in writing to Rwanda FDA, where the medical product is authorized. The notification shall be done as soon as possible and no later than 3 working days after establishing that a validated signal or a safety issue from any source meets the definition of an emerging safety issue.

The notification shall describe the safety issue, the source(s) of information, any planned or taken actions with timelines, and shall provide any relevant documentation available at the time of initial

notification. Any further information relevant to the issue should be provided to the Rwanda FDA as soon as it becomes available.

For signals notified as emerging safety issues, a standalone signal notification is not required, unless they consider it appropriate to handle the issue within Rwanda FDA signal management process, in which case the marketing authorization holder may be requested to complete and provide a standalone signal notification form (Annex 15).

Should the marketing authorization holder as a result of the emerging safety issue decide to suspend, withdraw or cancel marketing of their medicinal product, they shall notify Rwanda FDA in writing.

8.3 STANDALONE SIGNAL NOTIFICATION

After signal assessment, if a marketing authorization holder concludes that further analysis of the signal is required by Rwanda FDA, they should complete the standalone signal notification form and send it to the Authority. This should be done as soon as possible and no later than 30 days after the marketing authorization holder has completed their assessment and concluded that further analysis by the Authority is required.
Standalone signal notifications are not required in case of signals included within PSURs or variation applications, as per the conditions outlined in (Annex 15).

Signals contested by marketing authorization holders should not be sent as standalone signal notifications but should be included in PSURs/PBRERs as applicable.

8.4 EXCHANGE OF INFORMATION

Validated signals that may have implications for public health and the benefit-risk profile of the product in treated patients should be immediately communicated to Rwanda FDA and when appropriate, this should include proposals for action. Rwanda FDA should also communicate results of signal assessments to marketing authorization holders.
An essential feature of a signal management system, is that it is clearly documented to ensure that the system functions properly and effectively, that the roles, responsibilities and required tasks are standardized, that these tasks are conducted by people with appropriate expertise and are clear to all parties involved and that there is provision for appropriate control and, when needed, improvement of the system. Therefore, a system of quality assurance and quality control consistent with the quality system standards should be in place and applied to all signal management processes.

CHAPTER 9: PHARMACOVIGILANCE SYSTEM MASTER FILE(PSMF)

The Market Authorization Holders shall be required to maintain and make available a Pharmacovigilance system master file (PSMF) upon request by Rwanda FDA.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.

The PSMF shall be continuously accessible to the QPPV and to Rwanda FDA 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 into account of experience gained, technical and scientific progress and amendments to the legislative requirements.

Marketing authorization holders should be aware that immediate access to the PSMF may also be required by Rwanda FDA at the stated PSMF location or QPPV site (if different).The PSMF shall describe the pharmacovigilance system for one or more medical products of the MAH. For different categories of medical products, the MAH may, if appropriate, apply separate pharmacovigilance systems. Each system shall be described in a separate PSMF.

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. The QPPV shall be responsible for the establishment and maintenance of the pharmacovigilance system described in the PSMF.

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.

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 Rwanda FDA cannot contain multiple locations for a single PSMF.

When delegating any activities concerning the pharmacovigilance system and its master file, the marketing authorization holder shall retain the ultimate responsibility for the pharmacovigilance system, submission of information about the PSMF location, maintenance of the PSMF and its provision to Rwanda FDA 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.

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 Rwanda FDA 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.

9.1 OBJECTIVES

The objectives of PSMF are to provide an overview of the pharmacovigilance system, which may be requested and assessed by Rwanda FDA 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 fulfillment of supervisory responsibilities of the QPPV, and of inspections or other verification of compliance by Rwanda FDA.

Through the development and maintenance of the PSMF, the marketing authorization holder and the QPPV shall be able to:

a) gain assurance that a pharmacovigilance system has been implemented in accordance with the requirements;
b) confirm aspects of compliance in relation to the system;
c) obtain information about deficiencies in the system, or non-compliance with the requirements;

Obtain information about risks or actual failure in the conduct of specific aspects of pharmacovigilance.

9.2 STRUCTURES AND PROCESSES

PSMF is applicable for any medical products authorized in Rwanda. The required content and management of the PSMF applies irrespective of the organizational structure of a marketing authorization holder, including any subcontracting or delegation of activities, or their location.

Irrespective of the location of other activities, the qualified person for pharmacovigilance (QPPV's) residence, the location at which he/she carries out his/her tasks and the PSMF location must be in Rwanda or in the EAC region. The content of the PSMF should reflect global availability of safety information (If available /applicable) for medical products authorized in Rwanda or in the EAC region, presenting information on the pharmacovigilance system applied at global, regional and/or local levels.

9.3 DOCUMENT AND RECORD CONTROL

A description of the archiving arrangements for electronic and/or hardcopy versions of the PSMF should be provided, as well as an overview of the procedures applied to other quality system and pharmacovigilance records and documents:

a) 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 global, regional or local level within the organization, and the controls that are applied to their accessibility, implementation and maintenance.
b) Information about the documentation systems applied to relevant procedural documents under the control of third parties.
c) 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 the detailed guidance.

9.4 AUDITING

Information about quality assurance auditing of the pharmacovigilance system shall be included in the PSMF. A description of the approach used to plan audits of the pharmacovigilance system and the reporting mechanism and timelines should be provided, with a current list of the scheduled and completed audits concerning the pharmacovigilance system maintained in the annex. This list should describe the date(s)(of conduct and of report), scope and completion status of audits of service providers, specific pharmacovigilance activities or sites undertaking pharmacovigilance and their operational interfaces and cover a rolling 5 year period.

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 should also describe the process for recording, managing and resolving deviations from the quality system; pharmacovigilance procedures, their impact and management until resolved. Audit trail should also allow traceability of how validated signals have been investigated.

9.5 MARKET AUTHORIZATION AND MAINTENANCE

A summary of the applicant's pharmacovigilance system shall be included in the marketing authorization application, which shall include the following in the dossier:

a) Proof that the applicant has a designated qualified person responsible for pharmacovigilance;
b) The Partner States in which the qualified person resides and carries out his/her tasks;
c) The contact details of the qualified person;
d) A statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities;
e) A reference to the location where the PSMF for the medical product is kept.
f) Pharmacovigilance plan (For details refer to the chapter 10)

9.6 CHANGES TO AND TRANSFER OF RESPONSIBILITIES FOR THE PSMF

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 by the QPPV. The types of changes that should be routinely and promptly notified are:

a) Updates to the PSMF or its location;
b) The addition of corrective and/or preventative actions (e.g. following audits and inspections).
c) Changes to content that fulfil the criteria for appropriate oversight of the pharmacovigilance system (in terms of capacity, functioning and compliance);
d) Changes in arrangements for the provision of the PSMF;
e) Transfer of significant services for pharmacovigilance to a third party (e.g. outsourcing of PSUR production);
f) Inclusion of products into the pharmacovigilance system for which the QPPV is responsible;
g) 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.
h) Transfer or delegation of responsibilities.

Following the transfer of responsibilities, the recipient QPPV shall explicitly accept the transfer of responsibility for a pharmacovigilance system in writing. The QPPV should be in a position to ensure and verify that the information contained in the PSMF is an accurate and up to date reflection of the pharmacovigilance system under his/her responsibility.

9.6.1 Contents of the pharmacovigilance system master file

The PSMF shall include documents to describe the pharmacovigilance system. Where there is no marketing authorization (and master file) previously existed in Rwanda, there may be information that cannot be initially provided, for example, compliance information. However, descriptions of what will be implemented shall be provided instead. The contents of the PSMF shall be as in the (Annex 10).

9.6.2 Change control, logbook, versions and archiving

The MAHs shall implement change control systems and have robust processes in place to continuously be informed of relevant changes in order to maintain the PSMF accordingly. The MAHs shall submit information about important changes to the pharmacovigilance system

including:

a) 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;
b) Changes in the provision of significant services for pharmacovigilance, especially major contractual arrangements concerning the reporting of safety data;
c) Organizational changes, such as takeovers, mergers, and the sites at which pharmacovigilance is conducted or the delegation/transfer of PSMF management.
d) Changes to the PSMF should be recorded in the logbook, such that a history of changes is available (specifying the date and the nature of the change). A record of the date and nature of notifications of the changes shall be made available to Rwanda FDA, the QPPV and relevant third parties should be kept in order to ensure that change control is fully implemented.
e) As a basis for audit and inspections, the PSMF provides a description of the pharmacovigilance system at the current time, but the functioning and scope of the pharmacovigilance system in the past may need to be understood.

9.6.3 Accessibility of the pharmacovigilance system master file

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.

The marketing authorization holder shall maintain and make available on request a copy of the PSMF. The marketing authorization holder must submit the copy not later than 7 days after receipt of the request from Rwanda FDA. The PSMF should be submitted in a readable electronic format or clearly arranged printed copy.

In the situation where the same PSMF is used by more than one marketing authorization holder (where a common pharmacovigilance system is used) the concerned PSMF should be accessible to each, as any of the applicable marketing authorization holders shall be able to provide the file to the Rwanda FDA within 7 days, upon request.

The PSMF may be requested on an ad hoc basis, particularly if a new pharmacovigilance system is being implemented, or if product specific safety concerns or issues related to the compliance with pharmacovigilance requirements have been identified.

9.6.4 Annex to the PSMF

An annex to the PSMF shall contain the following documents:

1. A list of medical products covered by the PSMF including the name of the medical product, the international non-proprietary name of the active substance(s), and countries in which the

authorization is valid. The list of medical products authorized in Rwanda should also include the authorization number(s).

2. The list should be organized per active substance and, where applicable, should indicate what type of product specific safety monitoring requirements exist (for example risk minimization measures contained in the risk management plan or laid down as conditions of the marketing authorization, non-standard PSUR periodicity).
3. For marketing authorizations that are included in a different pharmacovigilance system, for example, because the MAH has more than one pharmacovigilance system or third party agreements exist to delegate the system, reference to the additional PSMF(s) should also be provided as a separate list in the Annexes, such that, for a MAH, the entire product portfolio can be related to the set of PSMFs.
4. Where pharmacovigilance systems are shared, all products that utilize the pharmacovigilance system should be included, so that the entire list of products covered by the file is available. The products lists may be presented separately, organized per MAH. Alternatively, a single list may be used, which is supplemented with the name of the MAH(s) for each product, or a separate note can be included to describe the product(s) and the MAH(s) covered;
5. A list of written policies and procedures;
6. A list of contractual agreements covering delegated activities including the medicinal products;
7. A list of tasks that have been delegated by the qualified person for pharmacovigilance;
8. A list of all completed audits, for a period of five years, and a list of audit schedules;
9. A list of performance indicators where applicable;
10. A list of other PSMFs held by the same marketing authorization holder where applicable;
11. A list of document changes including at least the date, person responsible for the change and the nature of the change.

CHAPTER 10: PHARMACOVIGILANCE PLANNING

This section describes methods for summarizing the important identified risks of medical products, important potential risks, and important missing information, including the potentially at-risk populations and situations where the products are likely to be used that have not been studied preapproval. It proposes a structure for a pharmacovigilance plan and sets out principles of good practice for the design and conduct of observational studies.

10.1 SCOPE

Pharmacovigilance planning shall be useful for new medical products and health technologies as well as for significant changes in registered products (e.g., new dosage form, new route of administration, or new manufacturing process for a biotechnology-derived product)and for established products that are to be introduced to new populations or insignificant new indications or where a new major safety concern has a risen.

10.2 SAFETY SPECIFICATIONS

The safety specification shall provide a summary of the important identified risks of a drug, important potential risks, and important missing information. it shall also address the populations potentially at-risk, and outstanding safety questions that warrant further investigation to refine understanding of the benefit-risk profile during the post approval period.

The safety specification can be built initially during the premarketing phase and, at the time approval is sought, it shall reflect the status of issues that were being followed during development. The elements of the Safety Specifications: shall be as prescribed in ICH E2E PV planning guideline.

10.3 PHARMACOVIGILANCE PLAN

This section gives guidance on the structure of a pharmacovigilance plan. The plan shall be developed by sponsors/MAHs and will be discussed with Rwanda FDA.

Structure of the Pharmacovigilance Plan

The structure for the pharmacovigilance plan can be varied depending on the product in question and the issues identified in the safety specification. The structure shall contain the following:

a) Summary of Ongoing Safety issues
b) Routine Pharmacovigilance Practice
c) Action Plan for Safety issues
d) Summary of Actions to be completed, including milestones

The structure and details regarding PV plan shall be as prescribed in ICH E2E PV planning guideline.

10.4 PHARMACOVIGILANCE METHODS

The methods to address specific situations can vary, depending on the product, the indication, the population being treated and the issue to be addressed. The method chosen can also depend on whether an identified risk, potential risk, or missing information is the issue and whether signal detection, evaluation, or safety demonstration is the main objective of further study.

The various PV methods are described in (Annex 11) of these guidelines. The list is not allinclusive, and sponsors/MAHs shall use the most up-to-date methods that are relevant and applicable.

CHAPTER 11: PHARMACOVIGILANCE INSPECTIONS AND SELF-AUDITS

To ensure that MAHs comply with pharmacovigilance requirements and to facilitate compliance, Rwanda FDA will conduct routine or "for cause" Pharmacovigilance inspections. The results of an inspection will be routinely provided to the inspected MAH who will be given the opportunity to comment on the findings. The results will be used to help MAHs improve compliance and may also be used as a basis for enforcement action. The scheduling and conduct of these inspections will be driven by routine programs and by risk analysis criteria.

This chapter contains guidance on the planning, conducting, reporting and follow-up of pharmacovigilance inspections by Rwanda FDA and outlines the role of the different parties involved.;

11.1 THE OBJECTIVES OF PHARMACOVIGILANCE INSPECTIONS

The objectives of pharmacovigilance inspections are the following:

1. To determine that the MAH has personnel, systems and facilities in place to meet their pharmacovigilance obligations
2. To identify, record and address non-compliance which may pose a risk to public health;
3. To use the inspection results as a basis for enforcement action, where considered necessary.

Inspections can be announced, announced on short notice or unannounced. This will be determined by Rwanda FDA on case by case basis

11.2 TYPES OF INSPECTION

The types inspection in pharmacovigilance include Pre- and Post-authorization inspections.

Pre-authorization pharmacovigilance inspections are performed before a marketing authorization is granted and will be determined by Rwanda FDA case by case depending on the risk of the product.

Post-authorization pharmacovigilance inspections are inspections performed after a marketing authorization is granted and are intended to examine whether the marketing authorization holder complies with its pharmacovigilance obligations. The types of inspections as follows;

11.2.1 Pharmacovigilance System and product-related inspections

i) Pharmacovigilance system inspections are designed to review the procedures, systems, personnel, and facilities in place and determine their compliance with Rwanda FDA pharmacovigilance requirements. As part of this review, product specific examples may be used to demonstrate the

operation of the pharmacovigilance system.

ii) Product-related pharmacovigilance inspections are primarily focused 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).

11.2.2 Routine pharmacovigilance inspections

Routine pharmacovigilance inspections are inspections scheduled in advance as part of inspection Programmes. These inspections are usually system inspections but one or more specific products may be selected as examples to verify the implementation of the system and to provide practical evidence of its functioning and compliance. Particular concerns, e.g. raised by assessors, may also be included in the scope of a routine inspection, in order to investigate the specific issues.

11.2.4 Investigative or "for cause" inspections

For cause pharmacovigilance inspections are undertaken when a trigger is recognized, and an inspection is considered an appropriate way to examine the issues, this should be conducted through national or regional mechanisms. 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:
- Change in the risk-benefit balance where further examination through an inspection is considered appropriate;
- Delays or failure to identify or communicate a risk or a change in the risk-benefit balance;
- Communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to Rwanda FDA, as applicable;
- Non-compliance or product safety issues identified during the monitoring of pharmacovigilance activities by Rwanda FDA,
- Suspension or product withdrawal with no advance notice to Rwanda FDA,

c) reporting obligations (expedited and periodic):
- Delays or omissions in reporting;
- Poor quality or incomplete reports;
- Inconsistencies between reports and other information sources;

c) requests from Rwanda FDA
- Failure to provide the requested information or data within the deadline specified by Rwanda FDA;

- Poor quality or inadequate provision of data to fulfil requests for information from Rwanda FDA:

d) fulfilment of commitments:
   - Concerns about the status or fulfilment of risk management plan (RMP) commitments;
   - Delays or failure to carry out specific obligations relating to the monitoring of product safety, identified at the time of the marketing authorization;
   - Poor quality of reports requested as specific obligations; inspections:
   - Delays in the implementation or inappropriate implementation of corrective and preventive actions;
   - Information such as non-compliance or product safety issues from other types of inspections (GCP, GMP, GLP and GDP);
   - Inspection information received from regulatory authorities, which may highlight issues of non-compliance; others:
   - Concerns following review of the pharmacovigilance system master file;
   - Non-inspection related information received from other authorities, which may highlight issues of non-compliance;

Other sources of information or complaints.

11.2.5 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.

11.2.6 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 Rwanda 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 Rwanda FDA.

11.3 FREQUENCY

Domestic or Foreign MAH or any firms employed to fulfill marketing authorization holder's pharmacovigilance obligations shall be inspected once in 3 years respectively depending on the type of inspection to be performed.

Rwanda FDA 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. Rwanda FDA shall establish PV inspections programmes depending on the location of the MAHs.

There are several factors that need to be considered when establishing pharmacovigilance inspection programmes. These shall include but not limited to the following:

a) Compliance history and re-inspection date recommended during previous PV inspections,
b) Products with additional risk minimization activities, limited alternative in the market, with mass use and require PASS,
c) New MAHs/change in MAH or that which has never been inspected before and has many products Rwanda market. MAH whose products have safety concerns and availability of PV resources by MAH,
d) Changes in PV system e.g. change of QPPV, PV safety data base, contractual arrangements and transfer of PSMF.

11.4 SITESTOBE INSPECTED

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.

11.5 INSPECTION PLANNING

Pharmacovigilance inspections should be planned, coordinated, conducted, and reported on, followed-up and documented in accordance with inspection procedures outlined. A systematic and risk-based approach shall be used to prioritize the inspections.

11.6 PHARMACOVIGILANCE INSPECTION OBSERVATIONS

Pharmacovigilance inspection observations are classified as follows:

11.6.1 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 applicable legislation and guidelines.

11.6.2 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 applicable legislation and guidelines.

11.6.3 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.

11.7 INSPECTION FOLLOW-UP

When non-compliance with pharmacovigilance obligations is identified during an inspection, follow-up will be required until a corrective and preventive action plan is completed. The following follow-up actions should be considered, as appropriate:

a) Review of the marketing authorization holder's corrective and preventive action plan;
b) Review of the periodic progress reports, when deemed necessary;
c) Requests for submission of previously un-submitted data; submission of variations, e.g. To amend product information; submission of impact analyses, e.g. Following review of data that were not previously considered during routine signal detection activities;
d) Requests for issuing safety communications, including amendments of marketing and/or advertising information; requests for a meeting with the marketing authorization holder to discuss the deficiencies, the impact of the deficiencies and action plans;
e) Communication of the inspection findings to other NMRAs
f) Other product-related actions depending on the impact of the deficiencies and the outcome of follow-up actions (this may include recalls or actions relating to the marketing authorizations or clinical trial authorizations).

11.8 QUALIFICATION AND TRAINING OF INSPECTORS

Inspectors who are involved in the conduct of pharmacovigilance inspections required by Rwanda FDA should be officials, or appointed by Rwanda FDA in accordance with national regulation.It is recommended that PV inspectors are appointed based upon their experience and the minimum requirements defined by Rwanda FDA. In addition, consideration should be given to the recommendations for training and experience described in the Rwanda FDA procedures.
The inspectors should undergo training to the extent necessary to ensure their competence in the skills required for preparing, conducting and reporting inspections.

They should also be trained in pharmacovigilance processes and requirements in such way that they are able, if not acquired by their experience, to comprehend the different aspects of a pharmacovigilance system.

Documented processes should be in place in order to ensure that inspection competencies are

maintained. In particular, inspectors should be kept updated with the current status of pharmacovigilance legislation and guidance.

Training and experience should be documented individually and evaluated according to the requirements of the applicable quality system of Rwanda FDA.

11. 9 PARTICIPATION IN THE JOINT INSPECTIONS

Rwanda FDA will participate in EAC joint inspections initiated by EAC Secretariat in collaboration with Lead NMRA and other stakeholders. Rwanda FDA shall adopt the inspections outcomes from joint inspections carried out in and out of the country.

11.10 SELF-AUDITING

Marketing authorization holders 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 as listed in these guidelines and the respective pharmacovigilance legislation in each partner state. 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.

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.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.

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 Rwanda FDA during pharmacovigilance inspections.The risk-based audit shall be assessed in the following three stages:

11.10.1 Strategic level audit planning

The audit strategy is a high-level statement of how the audit activities will 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 will be performed including areas to be audited, methodology, assumptions, governance, risk management and internal controls of all parts of the pharmacovigilance system.

11.10.2 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.

11.10.3 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.

11.11 AUDIT REPORTING

a. 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 product related issues. The grading system shall be defined in the description of the quality system for pharmacovigilance.
b. The classification of the findings shall be as described in section 12.6 of these guidelines. 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 in an expedited manner.
c. The QPPV shall be notified of any audit findings relevant to the pharmacovigilance system in the Rwanda, irrespective of where the audit was conducted.
d. 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).

Actions and follow up

a) Corrective actions, including a follow-up audit of deficiencies, shall be taken where necessary.
b) The management of the organization shall be responsible for ensuring that 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.
c) 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.
d) The organization shall use performance indicators to continuously monitor the good performance of pharmacovigilance activities.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).

Auditors' qualifications, skills, experience and conduct

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

2. 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 should be treated with appropriate confidentiality and discretion.

11.12 OUTSOURCING

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.

11.13 RWANDA FDA, PHPs & HEALTH FACILITIES AUDITS

Rwanda FDA, Public Health Programmes and Health Facilities shall perform regular independent risk-based audits of their pharmacovigilance tasks and the quality system. The audits shall be conducted at regular intervals according to a common methodology to ensure that the quality system complies with the requirements.

Rwanda FDA shall conduct audits and supervision of the PV activities of the Public Health Programmes and Health Facilities to ensure that they meet their pharmacovigilance obligations.

CHAPTER 12: SAFETY COMMUNICATION

Safety communication refers to the exchange of real time information, advice and opinions between

experts and people facing threats to their health, economic or social wellbeing. The fundamental goal of safety 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.

Communicating safety information to patients and healthcare professionals is essential for achieving the objectives of pharmacovigilance. Promoting the rational, safe and effective use of medical products and minimizing risks contribute to the protection of patients and public health.

12.1 AIMS OF SAFETY COMMUNICATION

The aims of safety communication are:

a) Providing timely, evidence-based information on the safe and effective use of medical products and health technologies;
b) Facilitating changes to healthcare practices (including self-medication practices) where necessary;
c) Changing attitudes, decisions and behaviours in relation to the use of medical products and health technologies;
d) Supporting risk minimization behaviour;
e) Facilitating informed decisions on the rational use of medical products and health technologies.
f) In addition to the above effective, high-quality safety communication can support public confidence in Rwanda FDA system.

12.2 STEPS IN SAFETY COMMUNICATION

The risk communication process is a step by step process that involves the following:

a) Identifying the issue and its context
b) Assessing the risk and benefits
c) Identifying and analysing options
d) Selecting a strategy
e) Implementing the strategy
f) Monitoring and evaluation of results

Rwanda FDA shall communicate the risk related to medical products safety guided by the risk communication procedure for medicine safety.

12.3 PRINCIPLES OF SAFETY COMMUNICATION

The following principles of safety communication shall be applied:

a) 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.
b) 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.
c) 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.
d) There should be adequate co-ordination and cooperation between the different stakeholders involved in issuing safety communications (e.g. Rwanda FDA, PHPs, MoH, Health Facilities, and marketing authorization holders).
e) Information on risks shall be presented in the context of the benefits of the medicine and include available and relevant information on the seriousness, severity, frequency, risk factors, time to onset, reversibility of potential adverse reactions and expected time to recovery.
f) Safety communication shall address the uncertainties related to a safety concern. This is of particular relevance for new information which is often communicated while Rwanda FDA conducting their evaluations; the usefulness of communication at this stage needs to be balanced against the potential for confusion if uncertainties are not properly represented.
g) Information on competing risks such as the risk of non-treatment should be included where appropriate.
h) The most appropriate quantitative measures should be used when describing and comparing risks, e.g. the use of absolute risks and not just relative risks; when comparing risks, denominators should be the same in size. The use of other tools such as graphical presentation of the risk and/or the risk-benefit balance may also be considered
i) Patients and healthcare professionals should, where possible, be consulted and messages pretested early in the preparation of safety communication, particularly on complex safety concerns.
j) Where relevant safety communication should be complemented at a later stage with follow-up communication e.g. on the resolution of a safety concern or updated recommendations.
k) The effectiveness of safety communication should be evaluated where appropriate and possible.
l) Safety communications should comply with relevant requirements relating to individual data protection and confidentiality.

12.4 TARGET AUDIENCE

The primary target audiences for safety communication issued by Rwanda FDA and marketing authorization holders should be patients, care givers and healthcare professionals who prescribe, handle, dispense, administer or take medical products.

12.5 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:

a) Important new information on any authorized medical product which has an impact on the medicine's risk-benefit balance under any conditions of use;
b) The reason for initiating safety communication clearly explained to the target audience;
c) Any recommendations to healthcare professionals and patients on how to deal with a safety concern;
d) When applicable, a statement on the agreement between the marketing authorization holder and Rwanda FDA on the safety information provided;
e) Information on any proposed change to the product information (e.g. the summary of product characteristics (SmPC) or Package Information Leaflet (PIL));
f) Any additional information about the use of the medical product or other data that may be relevant for tailoring the message to the targeted audience;
g) 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;
h) A reminder of the need to report suspected adverse reactions in accordance with national spontaneous reporting systems.

12.6 COMMUNICATION CHANNELS

Relevant communication tools and channels should be considered when issuing a safety communication in order to reach the target audiences and meet their growing expectations. Different communication tools and channels shall include but not limited to:

a) Direct Healthcare Professional Communication (DHPC)
b) Communication materials from Rwanda FDA targeted at healthcare professionals
c) Information, Education and communication (IEC) materials to patients and the general public e.g. brochures, flyers, public alerts and others
d) Press communication e.g. press releases, press briefing
e) Website
f) Social media and other online communications
g) Bulletins and newsletters
h) inter-NMRA communication
i) Responding to enquiries from the public
j) Other means such as publications, scientific and professional journals
k) Conferences, seminars and workshops

12.7 EFFECTIVENESS OF SAFETY COMMUNICATIONS

Safety communication is considered effective when the message transmitted is received and

understood by the target audience in the way it was intended, and appropriate action is taken by the target audience. Mechanisms shall be introduced in order to measure the effectiveness of the communication. Research-based approach is recommended to be used to establish that safety communications have met the standards. This approach may measure different outcomes, including behavior, attitudes and knowledge.

12.8 SAFETY COMMUNICATION IN RWANDA

Safety communications shall follow the procedures described in the SOP.For medical products registered within EAC region, Rwanda FDA shall inform EACscreatariat and lead NMRA for public health protection.

The following safety announcements shall be conducted as perRwanda FDA communication channels:

a) The suspension, withdrawal or revocation of a marketing authorization due to changes to its risk benefit balance;
b) Restriction of indication or treatment population or the addition of a new contraindication;
c) Dissemination of a Direct Healthcare Professional Communication
d) Other emerging safety concerns judged by EAC Partner States NMRAs likely to give rise to public or media interest in the Partner States (e.g. a publication of important safety findings in a scientific journal, safety-related Regulatory action taken in a Partner State or in a country outside the EAC).

12.9 SAFETY COMMUNICATION FOR THE MAHs

When marketing authorization holder in Rwanda intends to make, a public announcement relating to information on safety concerns in relation to the use of a medical product, and in any event at the same time or before the public announcement is made, the marketing authorization holder shall be required to inform Rwanda FDA as per (Annex 13). The marketing authorization holder shall ensure that information to the public is presented objectively and is not misleading.
Rwanda FDA shall provide approval as early as possible but not later than 7 calendar days.

Whenever a marketing authorization holder becomes aware that a third party intends to issue communications that could potentially impact the risk-benefit balance of a medical product registered in Rwanda, the marketing authorization holder should inform Rwanda FDA and make every effort to share the content of the communication.

12.10 PUBLICATION OF DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION (DHPC)

Rwanda FDA may publish the final DHPC. The marketing authorization holder shall be informed of the intent to publish the DHPC so that the timing for such publication is aligned to the dissemination of DHPC. Rwanda FDA may also issue an additional safety announcement and

disseminate them to relevant healthcare professionals' organization as appropriate. This communication shall be in accordance with Direct health professional communication plan (Annex12).

CHAPTER 13: REGULATORY ACTIONS

13.1GENERAL CONSIDERATIONS

Rwanda FDA shall enforce relevant legislation and ensure compliance with pharmacovigilance requirements in order to protect public health. When non-compliance with pharmacovigilance requirements is detected, the necessary action will be judged on a case-by-case basis. Actions to be taken shall depend on the potential negative public health impact of non-compliance and instances of non-compliance may be referred for enforcement action.

In addition, in case of non-compliance, Rwanda FDA actions may include the following:

a) Education and Facilitation: stakeholders may be informed of non-compliance and advised on how this can be remedied.
b) Inspection: Non-compliant stakeholders may be inspected to determine the extent of non-compliance and then re-inspected to ensure compliance is achieved.
c) Rwanda FDA shall issue a formal warning letter reminding stakeholders of their pharmacovigilance obligations.
d) Naming non-compliant stakeholders: Rwanda FDA shall consider a policy of making public a list of stakeholders found to be seriously or persistently non-compliant.
e) Urgent Safety Restriction
f) Variation of the Marketing Authorization
g) Suspension of the Marketing Authorization
h) Revocation of the Marketing Authorization
i) Product recalls

13.2 WITHDRAWAL OF A PRODUCT FROM THE MARKET ON RISK-BENEFIT GROUNDS

After risk benefit evaluation of a product, the risks outweigh the benefits and the proposed risk minimization measures are considered inadequate to redress the balance, the medical product should be withdrawn from the market and Healthcare Professionals and Patients/the public should be informed as appropriate. In case the MAH withdraws the medical product due to safety concerns, they shall be obliged to immediately report to Rwanda FDA.

13.3 FUTURE CONSIDERATIONS

Rwanda FDA and stakeholders will aim at developing a vigilance framework on products that are currently not covered by these guidelines in the future. The products may include and not limited to antiseptics, disinfectants, blood and blood products, cosmetics, food and food supplements, nutraceuticals.

13.4 APPEAL

For products that have been suspended and/or cancelled marketing authorization by Rwanda FDA, MAH may make a written appeal to Rwanda FDA to review its decision.All notice of appeals must be made within thirty (30) calendar days from the date of the Rwanda FDA's notification.

MAH shall make appeal by giving grounds for review for each reason given for the rejection of his/herproduct. The grounds for the request shall be based on the information that was submitted in the product 's dossier and PSMF. Any additional or new information that was not earlier submitted will not be accepted. Rwanda FDA may review or uphold its earlier decision.

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ANNEXES

ANNEX 1: ADR/AEFI REPORTING FORM

Version 2019

RWANDA FDA
P.O. Box 84 Kigali
info@rwandafda.gov.rw
www.rwandafda.gov.rw

ADVERSE DRUG REACTION/ADVERSE EVENT FOLLOWING IMMUNIZATION REPORTING FORM

Type of Report	Severity of ADR/AEFI	Category of Suspected Product
Initial ☐ Follow up ☐	Serious ☐ Not Serious ☐	Medical product ☐ Vaccine ☐

I. PATIENT INFORMATION

Patient ID/initials _____ **Gender**: Male ☐ Female ☐ **Weight** (kg)_____

Height (m) _____ Pregnancy Status: **YES** ☐ **NO** ☐ **Date of birth** ____/____/____

Patient Address: Village _____ Cell _____

Sector _____ District: _____ Phone N° _____

Patient's Medical History (Provide any relevant medical history and laboratory results including dates (if done):

II. INFORMATION ON ADVERSE EVENT(S)

Brief description of the ADR/AEFI:

(a) Information on Onset:

Date of ADR/AEFI onset: ____ /_____/_____(dd/mm/yyyy)

Time of onset: _____/____/_____ (hours, Min, Sec)

Date ADR/AEFI stopped: _____/ ____/_____(dd/mm/yyyy)

(d) Adverse Event Evolution/ Outcome:

Recovered ☐ Recovering ☐ Recovered with sequelae ☐

Not recovered ☐ Congenital abnormality ☐ Death ☐ Unknown ☐

(b)Severity of the ADR/AEFI Mild ☐ Moderate ☐ Serious ☐ Unknown ☐

Reason for seriousness: Prolonged hospitalization ☐ Disability ☐ Congenital abnormality ☐ Death ☐ Life threatening ☐

(e) Causality of the ADR/AEFI (If performed):

Certain ☐ Probable/Likely ☐ Possible ☐ Unlikely ☐ Unclassifiable ☐

(c) Action Taken:

Drug withdrawn ☐ Dose increased ☐ Dose reduced ☐ Dose not changed ☐

Substituted ☐ Antidote ☐ **Other** ☐ *(Specify):* .....

(f) Optional information:

☐ Therapeutic Failure *(Provide information on medicine (s) or vaccine (s) that showed lack of efficacy*.....

☐ Medication errors *(Provide details of medication errors)*

III. INFORMATION ON SUSPECTED PRODUCT

A. Details of suspected medicinal product **Source/Supplier:**

Product brand name & manufacturer	Generic name/ /Strength/ Dosage form	Route of Administration	Dose and frequency	Starting Date and Time	Stopping Date and Time	Batch N°. & Expiry date	Indications (Reason for use)
Other medicines used at the same time and/ or in the last one month (including herbal medicines)							

B. Details of Suspected Vaccine **Diluent (if applicable)**

Name of vaccine	Date of vaccination	Time of vaccination	Dose (1st, 2nd, 3rd etc.)	Batch/Lot N° & Expiry date	Name of diluent	Batch/Lot N° & Expiry date	Date & time of re-constitution

IV. REPORTER INFORMATION

Name of reporter:		Qualification:		Phone number	
Health Facility Name:		District:		Report Reference N°	
E mail Address of Reporter		Contact/Tel N°.		Date of report:	

Note: Reporters and patients' identity are held in strict confidentiality by Rwanda FDA and protected to the fullest extent of the Law

ANNEX 2: PATIENT ADVERSE DRUG REACTIONS REPORTING FORM

Version 2019

RWANDA FDA
P O. Box 84 Kigali
info@ rwandafda.gov.rw
www.rwandafda.gov.rw

SUSPECTED ADVERSE DRUG REACTION PATIENT REPORTING FORM
IFISHI Y'UMURWAYI YO GUTANGIRAHO AMAKURU KU NGARUKA ZATEWE N'UMUTI

I. PATIENT INFORMATION/ AMAKURU KU MURWAYI

Patient ID/initials (Ibiranga umurwayi): …… Sex/Igitsina: Male/Gabo❑ Female/Gore ❑ Age of the patient/ Imyaka y'umurwayi: …… Weight/ Ibiro (kg):…… Height/ Uburebure (m): …… Pregnancy Status/ Kumenya niba atwite: **YES/YEGO❑ NO/OYA ❑**	**Patient Address/ Aho umurwayi abarizwa:** Village/Umudugudu:…… Cell/Akagali: …… Sector/Umurenge:…… District/Akarere: …… Phone/Telefoni N°:……

II. BRIEF DESCRIPTION OF THE ADVERSE DRUG REACTION/ INCAMAKE Y'INGARUKA ZATEWE N'UMUTI/IMITI

Describe how the medicines affected you /Vuga mu ncamake ingaruka zatewe n'umuti/imiti:…… …… ……	Starting date/ itariki byatangiriyeho: ……/……/…… Stopping Date (if known)/Itariki byahagarariyeho niba izwi): ……/……/…… Reporting Date/ Itariki yabivugiyeho……/……/……

ADR Seriousness/Severity (Tick as appropriate)/ Ubukana bw'ingaruka zatewe n'umuti/ imiti (Hitamo ikiri cyo):

❑ Discomfort but able to work (Utameze neza ariko ushobora gukora) ❑ Caused persistent disability or incapacity (Wateye ubumuga) ❑ Discomfort and not able to work (Utameze neza kandi udashobora gukora)	❑Caused a congenital anomaly (Zateje kubyara umwana ufite ubumuga) ❑Required or prolonged hospitalization (wateje gutinda mu bitaro) ❑Patient Died (Umurwayi yapfuye): Date of death/Itariki yapfiriyeho:……/……/…….. ❑Life threatening (Ingaruka zishyira ubuzima mu kaga) ❑Others, please give details (Izindi, sobanura)……

III. LIST OF MEDICINES TAKEN BY THE PATIENT / URUTONDE RW'IMITI UMURWAYI YAFASHE

Name of the Medicine / Izina ry'umuti	Strength / ingano y'umuti yafashe	Daily frequency of administration /inshuro ufatwa k'umunsi	Route of administration/ Aho umuti unyuzwa mu kuwufata *(mu kanwa, mu mutsi, etc)*	Starting date/ Igihe yawu-tangiriye	Stopping Date/ Igihe yawu-hagarikiye

DESCRIPTION OF ANY HERBAL MEDICINE TAKEN/Ibisobanuro ku miti gakondo (y'ibyatsi) umurwayi yafashe.

Please state the suspected medicine that caused adverse drug reaction /Vuga umuti ukeka ko wateje ingaruka:

SOURCE OF THE MEDICINE TAKEN BY THE PATIENT / AHO UMURWAYI YAKUYE UMUTI

❑ Health Facility /Ivuriro ❑Retail Pharmacy/Farumasi idandaza ❑ Wholesale Pharmacy/Farumasi iranguza ❑Family/Neighbor/Ku muvandimwe/umuturanyi ❑ Community Health Worker/Umujyanama w'Ubuzima ❑Traditional Healer/Umuvuzi gakondo ❑Others/Ahandi *(Please specify/havuge):* ……

IV. REPORTER NAMES AND CONTACT ADDRESS /AMAZINA N'AHO UTANZE AMAKURU ABARIZWA

Name: (Optional)/Izina (kubushake): ……Contact Address/Aho abarizwa: Akagali……
Umurenge……Akarere:……Contact Phone N°/Nimero ya telephone……
E-mail: (if available/Niba ihari):……Reporting Date /Itariki ya raporo:……

Thank you for your cooperation/Tubashimiye ubufatanye	***Ref No. (for official use)/Ahagenewe ubuyobozi***

ANNEX 3: MEDICAL DEVICES EVENT/INCIDENT REPORTING FORM

Version 2019

RWANDA FDA
P O. Box 84 Kigali
info@ rwandafda.gov.rw
www.rwandafda.gov.rw

MEDICAL DEVICE ADVERSE EVENT REPORTING FORM

Type of Report	**Category of event**
Initial ☐ Follow up ☐	Public health threat ☐ Death/Serious injury ☐ Other ☐

I. PATIENT INFORMATION

Patient ID/initials: ……**Gender**: Male ☐ Female ☐ **Weight**(kg)…… **Height** (m): ……Pregnancy Status: **YES** ☐**NO** ☐ **Date of birth**: ……/……/…… **Patient Address:** Village…… Cell: …… Sector: ……District:…… Phone N°:……	**Patient's Medical History** (Provide any relevant medical history and laboratory results including dates (if done): …… …… …… ……

II. INFORMATION ON ADVERSE EVENT(S)

Brief description of the Event:

(a) Information on Onset: Date of event onset: ……/……/……(dd/mm/yyyy) Time of onset: ……/……/…… (hours, Min, Sec) Date Event stopped:…… / ……/……(dd/mm/yyyy)	**(d) Patient Outcome:** Recovered ☐ Recovering ☐ Recovered with sequelae ☐ Not recovered ☐ Disability ☐ Death ☐ Unknown ☐
(b) Operator at Onset: Healthcare Professional ☐ Patient ☐ Caregiver ☐ N/A ☐	**(c) Usage of device (choose whichever applies):** Single use ☐ Reuse of Reusable ☐ Reuse of single use ☐ Reserviced/Refurbished ☐ Problem noted prior to use ☐ other (specify) ☐ …… Date of Implant: …. /…. /….. Date of Explant…../…../…… Device Disposition/Current location: …… Expiry date (if applicable):……
(c) Remedial Action/Corrective Action/Preventive Action: ……	

III. INFORMATION ON DEVICE

Brand name:	Common name:*(e.g. catheter; central venous, peripherally inserted*	
Model:	Catalogue:	Serial/Lot No:
Name of manufacturer:	Address:	

DIAGNOSTICS SECTION (for diagnostics only)

Type of specimen used (e.g. blood, saliva, etc.):		
Number of patients involved:	Number of tests done:	Number of false positives:
Number of false negatives:	Number of true positives:	Number of true negatives:

IV. REPORTER INFORMATION

Name of reporter:		Qualification:		Phone number	
Health Facility Name:		Report Reference N°			
E mail Address of Reporter:		Contact/Tel N°:		Date of report:	

Note: Reporters and patients' identity are held in strict confidentiality by Rwanda FDA and protected to the fullest extent of the Law

ANNEX 4: PRODUCT QUALITY REPORTING FORM

RWANDA FDA
P O. Box 84 Kigali
info@ rwandafda.gov.rw
www.rwandafda.gov.rw

Version 2019

SUSPECTED POOR QUALITY PRODUCT REPORTING FORM

I. PRODUCT CATEGORY (Tick as appropriate)

Medicinal product ☐ Vaccine ☐ Other Biological Products ☐ Herbal product ☐ Other *(Please Specify)*:
.....

II. PRODUCT DETAILS

Brand name				Generic Name			
Batch/Lot N°		Manufacturing Date		Expiry date		Date of receipt	
Name of manufacturer				Physical Address and Country of Origin			
Name of Distributor/ Supplier				Distributor/ Supplier's Address			

III. PRODUCT FORMULATION

☐ Tablets /capsules
☐ Suspension/Syrup
☐ Injectable/Infusions
☐ Creams/Ointment/Liniment/Paste
☐ Pessaries
☐ Suppository
☐ Powder for reconstitution of oral suspension
☐ Powder for reconstitution of injection
☐ Ear/Eye drops
☐ Diluents
☐ Nebulizing solutions
☐ Other *(Please Specify)* .....
.....

IV. DESCRIPTION OF PRODUCT COMPLAINT

☐ Color/odor change
☐ Molding
☐ Turbidity
☐ Mislabelling
☐ Poor Packaging/ lack of patient leaflet/ lack measuring devices
☐ Therapeutic ineffectiveness
☐ Particulate matter
☐ Seal Integrity of packs and/ or Leakage
☐ Caking
☐ Separating
☐ Incomplete packs
☐ Powdering/crumbling
☐ Suspected falsified/ Substandard
☐ Others *Specify)* .....

Describe the Complaint in details:
.....
.....

V. PRODUCT STORAGE CONDITIONS

Does product require refrigeration?	YES ☐ NO ☐	***Other Storage details** (if necessary):*
Does product require protection from light?	YES ☐ NO ☐	
Does product require protection from Moisture?	YES ☐ NO ☐	
Was it stored following manufacturer/Rwanda FDA guidelines?	YES ☐ NO ☐	

VI. CIRCUMSTANCE AND TIME OF THE POOR-QUALITY DETECTION

When did you notice the poor-quality problem?

☐ Before taking/administering the product
☐ While taking/administering the product
☐ After taking/administering the product
☐ When the patient returned the product

☐ After a complaint of the patient
☐ After Visual inspection
☐ After quality control
☐ Other (specify).....

VII. ACTION TAKEN

☐ Stop Taking/Administration of the product
☐ Quarantining the product
☐ Returning the product to the supplier
☐ Other (specify):.....

Have you experienced any adverse event after taking this medicine? **YES** ☐ **NO** ☐ **If YES**, please complete the ADR/AEFI Reporting Form.

VIII. REPORTER INFORMATION

Name of reporter:		Qualification:		Phone number:	
Name of Health Facility		District:		Report Reference No:	
E-mail Address:		Contact/Tel No:		Date of report:	

All information is held in strict confidentiality and will not disclose reporter's identity in response to any public request. Information supplied will contribute to the improvement of safety and vigilance of Medical Products in Rwanda. Once completed please send it to Rwanda FDA.

ANNEX 5: ADVERSE DRUG REACTION ALERT CARD

Version 2019

RWANDA FDA
Rwanda Food and Drugs Authority
P O. Box 84 Kigali
info@rwandafda.gov.rw
www.rwandafda.gov.rw

ADVERSE DRUG REACTION ALERT CARD

PATIENT NAME: .....

ID/PASSPORT N°:.....**TEL**.....

AGE: ..... **GENDER:** .....**BLOOD GROUP:** .....

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

RESPONSIBLE DRUG(S): .....

.....

.....

DESCRIPTION OF REACTION: .....

.....

.....

.....

Names, Signature and stamp of the Medical Doctor

.....

Please carry this card with you at all times and remember to show it to your health care provider at each time of consultation	***Ibuka kwitwaza iyi karita igihe cyose no kuyereka muganga igihe ugiye kwivuza***

Rear side

CRITERIA FOR ISSUE OF ADVERSE DRUG REACTION ALERT CARD

The alert card is to be 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.

ANNEX 6: FORMAT OF A RISK MANAGEMENT PLAN

OVERVIEW OF THE RMP PARTS AND SECTIONS

Part I Product(s) overview
Part II Safety specification
Section I Epidemiology of the indication(s) and target population(s)
Section II Non-clinical part of the safety specification
Section III Clinical trial exposure
Section IV Populations not studied in clinical trials
Section V Post-authorization experience
Section VI Additional Rwanda FDA requirements for the safety specification
Section VII Identified and potential risks
Section VIII 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

PART I: PRODUCT OVERVIEW

This section should provide information on the RMP and the overview of the product. This should 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 of medicinal product(s) to which this RMP refers, Authorization procedure(s) (centralized, mutual recognition), and brief description of the product including:

a) Chemical class;
b) Summary of mode of action;
c) Composition (e.g. Origin of active substance of biologicals, relevant adjuvants or residues for vaccines);
d) Indications
e) Pharmaceutical form and strengths

PART II: 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:

a) Epidemiology of the indication(s) and target population(s)
b) Non-clinical part of the safety specification
c) Clinical trial exposure
d) Populations not studied in clinical trials
e) Post-authorization experience
f) Additional Rwanda FDA requirements for the safety specification
g) Identified and potential risks
h) Summary of the safety concerns
i) Pharmacovigilance plan (including post-authorization safety studies)

Refer to chapter 7 PV Plan and chapter 11 PASS of the guideline and Current version of ICH PV planning E2E

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.

RMP ANNEXES

a) Tabulated summary of planned, on-going, and completed pharmacovigilance study programme
b) Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan
c) Specific adverse event follow-up forms
d) Protocols for proposed and on-going studies in RMP part IV
e) Details of proposed additional risk minimization activities
f) Other supporting data (including referenced material)
g) Summary of changes to the risk management plan overtime

ANNEX 7: FORMAT OF THE PROTOCOL FOR NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDIES

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.15August2018). Annex1should 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 a part 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.

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 information**: PASS 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) (ATC 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
Marketingauthorization 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 the PASS protocol submission (if it is a joint PASS, only one person should be mentioned)

3. Table of contents (PASS):

The study protocol should include a table of contents.

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 should be provided. Contact details and the list of all investigators can be kept in a stand-alone document to be listed and available up on 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.)

4. Abstract:

Stand-alone summary of the study protocol shall include the following subsections

a) Title: The title should include subtitles including version and date of the protocol

b) Name and affiliation of main author

c) Rationale,background, Research question,objectives, Study design and study population. ("Population" includes the setting and study population.)

d) Variables, Data sources and Study sample size

e) Data analysis

f) Milestones

5. 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
3	Date	Text	Text	Text

6. 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 data bases such as claims, prescriptions or health care records, "secondary use of data" applies to these definitions). Other important timelines can be added.

Milestone	Planned date
Start of data collection	Date
End of data collection	Date
<Study progress report 1>	Date
<Study progress report 1>	Date
<Study progress report 1>	Date
<Interim report 1>	Date
<Registration in the EU PAS register>	Date
Final report of study results	Date

7. Rationale and background:

Short description of the safety hazard(s), the safety profile or the risk management measures that led

to the initiation or imposition of the study, and short critical review of available published and unpublished data to explain gaps in knowledge that the study is intended to fill. The review may encompass relevant animal and human experiments, clinical studies, vital statistics and previous epidemiologic studies. The review should cite the findings of similar studies, and the expected contribution of the current study.

8. Research question and objectives:

Research question that explains how the study will address the issue which led to the study being initiated or imposed, and research objectives, including any pre-specified hypotheses and main summary measures. Objectives should be organized as primary or secondary objectives where applicable.

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

a) 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.

b) 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.

c) 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.

d) Data sources: Strategies and data sources for determining exposures, outcomes and all other variables relevant to the study objectives, such as potential confounding variables and effect modifiers should be specified. Where the study is based on secondary analysis of 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.

e) Study sample size: Any projected study sample size, precision sought for study estimates and any calculation of the sample size that can minimally detect a pre-specified risk with a pre-specified statistical precision. All assumptions used to calculate the study size or precision of the study should be presented and justified.

f) Data management: Data management and statistical software(s) to be used in the study, including procedures for data collection, retrieval, 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.

g) 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, analyse, present results, procedures to control sources of bias and their influence on results. Statistical procedures to be applied for obtaining point estimates and confidence intervals of measures of occurrence or association, and sensitivity analyses should be specified.

h) Quality control: Description of any mechanisms and procedures to ensure data quality and integrity, including accuracy,legibility of collected data,original documents, extent of source data verification, 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.

i) Limitations of the research methods: Any potential limitations of the study design, data sources, and analytic methods, including issues relating to confounding, bias, generalizability, and random error should be specified. The likely success of efforts taken to reduce errors should be discussed.Other aspects: Any other aspect of the research method not covered by the previous sections should be specified.

9. Protection of human subjects:

Safeguards in order to comply with national requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.

10. 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.

10. Plans for disseminating and communicating study results:

Any plans for submission of progress and final reports; any arrangements made between marketing authorizations holders for the disseminating andcommunicating study results of Joint PASS should be provided.

11. References:

Numbered list of literature or electronic references of documents referred to in the protocol should be specified. Sufficient information should be provided to allow retrieval of the document. Feasibility or pilot studies that were carried out to support thedevelopment 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 Rwanda FDA upon 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.

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

ANNEX 8: FORMAT OF THE PASS 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 PASS 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 should be specified.
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 should be specified. 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 Rwanda FDA and national competent authorities.
5. **Milestones**: dates for the following milestones should be specified:
    a. Start of data collection (planned and actual dates)
    b. End of data collection (planned and actual dates) or date of early termination, if applicable, with reasons for termination
    c. Study progress report(s)
    d. Interim report(s) of study results, where applicable
    e. Final report of study results (planned and actual date)
    f. Any other important milestone applicable to the study, including date of study registration in the Register and date of protocol approval.
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**: Study design: key elements of the study design and the rationale for the choice.
    a) **Setting**: setting, locations, and relevant dates for the study, including periods of recruitment, follow-up, and data collection should be specified. In case of a

systematic review or meta-analysis, study characteristics used as criteria for eligibility, with rationale should be specified.

b) **Subjects**: any source population, eligibility criteria of study subjects, sources and methods of selection of participants, relevant methods for case ascertainment, number and reasons for dropouts should be provided.

c) **Variables**: all outcomes, exposures, predictors, potential confounders, and effect modifiers, including operational definitions and diagnostic criteria, if applicable should be provided.

d) **Data sources and measurement**: for each variable of interest, sources of data and details of methods of assessment and measurement should be provided. 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 should be provided.

e) **Bias**: any efforts to assess and address potential sources of bias at the design stage should be reported.

f) **Study sample size**: study sample size, rationale for any study sample size calculation and any method for attaining projected study size should be reported.

g) **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 should be specified

h) **Statistical methods**: description of the following items are required:

   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.

Quality control: mechanisms to ensure data quality and integrity should be reported.

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:

a) 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 analysed, 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.

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

c) Outcome data: numbers of participants across categories of main outcomes.

d) Main results: unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). If relevant, estimates of relative risk should be translated into absolute risk for a meaningful time period.

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

f) Adverse events and adverse reactions: summary of all adverse events/adverse drug reactions collected in the study, in line with requirements described in these guidelines.

11. Discussion: The following key parameters shall be provided:

a) 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.

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

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

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

e) 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 9: METHODOLOGICAL ASPECTS OF SIGNAL DETECTION FROM SPONTANEOUS REPORTS OF SUSPECTED ADVERSE REACTIONS

Monitoring of databases of spontaneously reported suspected adverse reactions (in the format of individual case safety reports (ICSRs) is an established method of signal detection. The monitoring process is facilitated by statistical summaries of the information received for each "drug-event" combination over defined time periods. To limit the chances of failing to detect a signal and to ensure that the processes in place are controlled and predictable in terms of resources required, it is recommended that these summaries are produced in a routine periodic manner. For the same reasons, when possible, the criteria for selecting "drug-event" combinations (DECs)for further investigationshould be objectively defined. The aim of this Appendix is to describe components of an effective system for routine scanning of accumulating data focusing on components that have been proved to be effective.

This Appendix lists some of the methodological aspects that should be considered in detecting potential signals. The proposed approach complements the classical disproportionality analysis with additional data summaries, based on both statistical and clinical considerations. Although disproportionality methods have been demonstrated to detect many adverse reactions before other currently used methods of signal detection, this is not true for all types of adverse reactions. Hence, a comprehensive and efficient routine signal detection system will seek to integrate a number of different methods to prioritize DECs for further evaluation.
The specific details of implementation for methods proposed may vary depending on, for example, the nature of the medicinal products in the dataset or the rate at which new ICSRs are received. A general principle is that any system of signal detection should be monitored not only for overall effectiveness but also for the effectiveness of its components (e.g. statistical methods and specific group analyses).

I. Statistical methods

When the accumulation to the database is too large to allow individual scrutiny of all incoming ICSRs, it is useful to calculate summary statistics on (subsets of) the data that can help to focus attention on groups of ICSRs containing an adverse reaction. Generally, such statistics are used to look for high proportions of a specific adverse event with a given medicinal product,compared to the reporting of the event for all other medicinal products (disproportionate reporting). Sudden temporal changes in frequency of reporting for a given medicinal product may also indicate a change in quality or use of the product with adverse events (which could include a reduction in efficacy).

II. Disproportionate reporting

Disproportionality statistics take the form of a ratio of the proportion of spontaneous ICSRs of a specific adverse event with a specific medicinal product to the proportion that would be expected if no association existed between the product and the event. The calculation of the expected value is based on ICSRs that do not contain the specific product and it is assumed that these ICSRs contain a diverse selection of products most of which will not be associated with the event. Hence, the

reporting proportions for events in these ICSRs will reflect the background incidence of the event in patients receiving any medicinal product. There are a number of different ways to calculate such statistics and this choice is the first step involved in designing a statistical signal detection system.When an adverse event is caused by a medicinal product, it is reasonable to assume that it will be reported more often (above the reporting rate associated with the background incidence), and hence the reporting ratio will tend to be greater than one. Thus, high values of the ratio for a given DEC suggest further investigation may be appropriate. In practice a formal set of rules, or signal detection algorithm (SDA) is adopted. This usually takes the form of specified thresholds that the ratio or other statistics must exceed, but more complex conditions may also be used. When these rules are satisfied for a given DEC, it is called a signal of disproportionate reporting (SDR). Then a decision needs to be made regarding whether further investigation is required.
A further decision needs to be taken as to whether the statistics are to be calculated across the whole database or if modifications based on sub grouping variables would be of value. While the decision is motivated by theoretical consideration, the specific choice of whether to use subgroups and, if so, which to use, should be based on empirical assessment of signal detection performance. In particular, the impact on the false positive rate should be considered. Whether the database is sufficiently large to avoid very low case counts with in subgroups may also be a factor in this decision.

1. Considerations related to performance of signal detection systems
2. The performance of signal detection systems, including the SDA, can be quantified using three parameters that reflect the intended objective of the system. Desirable properties are:
3. high sensitivity (the proportion of adverse reactions for which the system produces SDRs);
4. high positive predictive value or precision (the proportion of SDRs that relate to ad- verse reactions);
5. Short time to generate SDRs (that can be assessed from a chosen time origin, possibly the granting of a marketing authorization to the first occurrence of an SDR for an adverse reaction).
6. Estimates of these performance parameters depend on the particular reference set of known ad- verse reactions selected for their evaluation and are also not fixed because spontaneous reports accumulate over time. They are thus, best used as relative measures for comparing competing methods of signal detection within the same spontaneous reporting system at the same point in time.

The following factors may affect the performance of signal detection systems:

1. MedDRA hierarchy

A precondition for automated screening of DECs for adverse reactions is the availability of schemes for classifying adverse events and medicinal products. The nature and granularity of these schemes affects the performance of the screening. MedDRA used for reporting suspected adverse reactions purposes, provides terms for adverse events and classifies the minima multi-axial hierarchical structure and a choice must be made whether to screen at one level of granularity (e.g. SOC, HLT, PT) or several and whether to include all terms or only a subset. Screening at the second finest level

of granularity, i.e. Preferred Term (PT), has been shown to be a good choice in terms of sensitivity and positive predictive value.
Finally, focus of statistical signal detection on adverse events considered clinically most important avoids time spent in assessments that are less likely to benefit patient and public health. A sub set of MedDRA terms judged to be important medical events (IMEs) is thus considered a useful tool in statistical signal detection when filtering results for medical review.
The remarks related to routine signal detection and not to targeted monitoring of potential risks associated with specific products where adhoc use of other levels of MedDRA terms may be appropriate. In addition, although no formally defined MedDRA term subgroups (e.g. HLT, SMQ) have proven better for signal detection than PTs, some of them are effectively synonymous. The definition of a synonym in this context is the pragmatic one, i.e. that two PTs are considered synonyms if it is reasonable to suppose that a primary reporter of a suspected adverse reaction, presented with a single patient and without a specialist evaluation, would not necessarily be able to decide which term to use. It may also be appropriate to combine such terms when they relate to identified areas of interest.

2. Thresholds

The SDA applied to the summary statistics for each DEC usually takes the form of a set of threshold values such that SDRs occur only if each statistic exceeds its corresponding thresh- old. Very low thresholds will result in large, and potentially unmanageable, numbers of SDRs toinvestigate with a higher probability of being false. This will also reduce the resources avail- able for assessment of true SDRs. Too high thresholds will result in identification of adverse reactions being delayed or even entirely prevented. Thus, the appropriate choice of thresholds is fundamental to the success of the statistical signal detection system.
This has also been confirmed by studies comparing different disproportionality methods and different sets of thresholds showing that the former can achieve similar overall performance by choice of appropriate SDA. Therefore, in contrast to the choice of disproportionality statistic, it is the choice of SDA to define a SDR that will strongly influence signal detection performance.

Thresholds for disproportionality methods are usually based on two separate indicators, one reflecting the disproportionality statistic itself and another based on the number of ICSRs received. For a reason discussed later, limiting false positives is better handled by raising the threshold for the number of ICSRs than that for the disproportionality statistic. For the disproportionality statistic, in practice, rather than the point estimate, a formal lower confidence bound is often used. The rationale for its use is that when the statistic is based on few ICSRs, it falls further below the point estimate and makes an SDR less likely. Hence, this is an spontaneous way of incorporating into the signal detection process the degree of confidence about the reliability of the data. It has also been shown that a threshold based on the lower confidence bound is performed better alone than with an additional threshold for the absolute value of the disproportionality statistic itself.
In addition, it has been shown that a correlation exists between the value of a disproportionality statistic and the relative risk of an adverse reaction when exposed to the medicinal product estimated

in epidemiological studies, therefore setting any threshold on the lower confidence bound of the disproportionate statistic above 1 might lead to missing an adverse reaction for which the risk ratio is not high.

Finally, there appears to be a reduction in positive predictive value with a medicinal product's time on the market, hence it might be more efficient to vary the amount of effort to invest in signal detection over the life-cycle of the product. This might involve the use of different thresholds to define an SDR depending on the time of the product on the market.

3. Periodicity of monitoring

A one-month interval between consecutive data summaries has been investigated in validation studies for signal detection methods. More frequent monitoring has also been used, for instance for medicinal products under additional monitoring or during intensive vaccination programmes. The appropriate frequency of monitoring may vary with the accumulation of knowledge of the risk profile of a specific active substance/medicinal product.

4. Spontaneous ICSR databases

The performance has also been shown to depend on the nature of the spontaneous ICSR data- base and this appears to be related to the range of medicinal products included in the database.
An important inference from these considerations is that organizations doing signal detection should assess the performance of a signal detection system directly on the database to which it will be applied. This will allow the ability to detect new adverse reactions and the work load involved to be predicted and controlled by appropriate changes to the SDA. As databases evolve
in terms of numbers of ICSRs included and their mix of medicinal products, periodic reassessment of performance should be undertaken.

5. Subgroup analysis and stratification

Spontaneous ICSR databases cover a range of medicinal products with different indications and that are used across a broad range of patient populations. Also, ICSR reporting patterns vary over time and between different geographical regions. Many quantitative signal detection algorithms disregard this diversity which may result in an SDR either being masked or in an association being incorrectly flagged as a signal.Stratification and subgroup analysis are generally used in epidemiology to reduce bias due to confounding and may also have advantages in statistical signal detection. By subgroup signal detection here is meant analyses carried out to detect ADRs within specific ICSR subgroups e.g. by indication, age group, region or time period. Stratification involves combining results from within different subgroups to obtain an adjusted result for the whole dataset. The comparison of stratified versus subgroup analysis has shown that the subgroup analysis consistently performed better. Moreover, subgroup analysis has also shown to provide clear benefits in both sensitivity and precision over crude analyses for large international databases. However,

such benefits may not be obtained in small databases.

Sub-grouping variables that showed the most promising results included age and reporting region/country, but it is likely that choice of variables for subgroup analyses varies according to the database.

6. Increased ICSR reporting frequency

Most routine signal detection is aimed at identifying unknown, potentially causal associations between medicinal products and adverse events that are assumed to be constant over time. However, some causal associations of medicinal products with events of interest in the context of pharmacovigilance may show a marked temporal variation. Examples are manufacturing quality issues, a developing culture of abuse, evolving antimicrobial resistance or changes in the use of the product and, in particular, new off-label use. One way of detecting signals associated with such events, that may add value to simple disproportionality methods, is to monitor changes in the frequency of overall reporting for the products.

However, changes of reporting frequency are also expected that do not reflect new safety issues of the medicinal products. These may result from rapid increases in use when the product is first marketed or new indications are authorized, sudden changes in exposure (e.g. seasonal use of vaccines), publicity associated with unfounded safety concerns, reporting promoted by patient

support schemes not clearly labelled as studies, clusters of ICSRs reported in the scientific literature or duplicated ICSR reports.

There are several options for detecting temporal changes in reporting frequency. The simplest method examines the changes in the number of ICSRs received per product over a fixed time period as an absolute count. Statistical tests compare recent counts with the latest count, testing for significant increases. Similar methods can be used at the DEC level and, for these, relative values compared to the total ICSR count for the product may be considered as an alternative to absolute counts. The method disregards however, quantitative changes in exposure, which would impact on the frequency of adverse reactions.

Another option is to consider changes in the disproportionality statistics over time. This approach is less susceptible to increase in number of ICSRs triggered by effects related to the product rather than a specific adverse event for example, general publicity about the product, stimulated reporting or changes in exposure. However, results will still be influenced by the background distribution in the rest of the database by changes in reporting frequency for the specific medicinal product. In addition, results might be less reactive to transient temporal variations since the focus is on changes in statistics based on the cumulative count, not in comparing recent counts with the latest count. This problem will be more pronounced when large numbers of cases have accumulated, as proportional changes will then be smaller.

Limited work has been performed to assess the effectiveness of these methods even if theoretically they seem appealing. Thus, these methods might be implemented with ongoing quality control measures to ensure acceptable performance.

a. Methods aimed at specific groups of adverse events
b. Designated medical events

Some medical events are known to result on most occasions from exposure to medicines. Thus, when such events are reported, the prior probability of a causal relationship to one of the medicinal products listed in the ICSR is high. Hence the ICSRs will evoke concerns even before an SDR is observed. A list of these terms, complemented by important and serious events that should not be missed, should then be created and can serve as a safety net in signal detection. It is recommended that these designated medical events (DME) are drawn to the attention of signal detection assessors irrespective of any other statistical methods used and that they are prioritized for clinical review. Elements of the DME list are generally small subset of the IME list. The list of DME should also be periodically reviewed based on experience gained and performance.

7. Serious events

The seriousness of events described in spontaneous ICSRs does not obviously relate to the probability that they are causally related with the medicine. However, it may impact the patient and public health. This reason is a rationale for prioritizing assessment of serious events. Complementary to the creation of a list of DMEs and in addition to the use of lists of IMEs, a simple approach to such prioritization is to highlight new ICSRs in which a death is reported and to give separate counts of those ICSRs for each DEC. It should be appreciated that this may be a rather imprecise criterion and prioritizing all ICSRs with reported death may result in many false positive signals. Hence, it is considered that further methodological research may be required in this area.

8. Methods aimed at specific patient populations

When ICSR databases are sufficiently large, some group of patients may be identified that merit separate attention in signal detection due to known or suspected systematic differences in their responses to medicines. Two such groups that can be differentiated in most databases are the youngest and oldest patients.

A caveat relevant to analyses restricted to any subset of spontaneous ICSRs is that homogeneity of adverse events may be increased resulting in greater potential for masking of signals. For example, analyses within a group of patients who are the main recipients of a class of medicines may not highlight effects related to the entire class. A possible solution is to monitor specific patient groups in parallel to analyze the total population.

a) Pediatric population

Often a single pediatric group is chosen below a selected age threshold. Although childhood is a period of rapid change and no threshold is likely to define a homogenous group, this succeeds in defining a population with marked developmental, physiological and psychological differences from adults.

Separate presentation of suspected adverse reactions that are detected in the pediatric population and use of both clinical and statistical methods seem to be justified to improve the detection of signals for the pediatric population. Statistical disproportionality tools should be applied to ICSRs reported for children to increase the ability to detect signals in the pediatric population from spontaneous ICSR databases. Within-group, disproportionality statistics that are significantly higher than those in the non-pediatric group should be highlighted for additional consideration. Additionally, given the lower number of ICSRs usually received for the pediatric population compared to the adult population, it is recommended to use a lower threshold based on the number of ICSRs received.

An additional aid to focusing on pediatric safety issues can be provided by a list of adverse events (a targeted medical events list) that tend to have more serious outcomes in children

than adults. This list should be used to reduce missed signals that are more clinically relevant in the pediatric population, otherwise not flagged by other methods. The age threshold for pediatric signal detection should be chosen to align with the upper age limit from this guideline.

b) Geriatric population

Specific signal detection measures aimed at older recipients of medicines area reasonable pre-caution given the high frequency of concomitant use of multiple medicines and the possibility of impaired physiological elimination mechanisms.

The age threshold at which such measured should be implemented has not been clearly established. Although the proportion of patients for whom suspected adverse reactions are reported increases with age, some research has suggested that this can be explained by more common use of medicines. Thus, it may be better to choose a threshold based on increased exposure rather than possible increased susceptibility. Alternatively, a consistent approach is to use the same age group in routine signal detection as selected for other pharmacovigilance activities.

For routine signal detection processes, it is recommended that ICSRs from patients above the chosen age threshold should be clearly identified and that, as for the pediatric population, within-group disproportionality statistics that are significantly higher than those within the non-geriatric group should be highlighted for additional consideration.

9. Methods aimed at specific circumstances of medicines use

In addition to the description of the clinical manifestation of the suspected adverse reaction, ICSRs may include information on the circumstances of medicine use which could have contributed to the occurrence of the adverse reaction, e.g. abuse, misuse, overdose, medication error or occupational

exposure.

Although the coding of these circumstances is enabled as Preferred Terms in MedDRA, they are qualitatively different from the clinical circumstances which are the focus of disproportionality-based signal detection. Firstly, they are manifestly related to at least one medicinal product identified in the ICSR. With suspected adverse reactions in normal circumstances of use, this relationship is a matter of clinical judgment. Secondly, the circumstances described by each of these terms differ depending on the product concerned. Hence, between medicine comparisons of reporting frequency of ICSRs with MedDRA-codes describing these circumstances are both unnecessary and potentially misleading.

However, knowledge of these circumstances can appreciably alter the assessment of causality when reviewing a potential signal. Thus, it is recommended that the numbers of ICSRs with the respective MedDRA codes should be displayed for each DEC.

The Rwanda FDA procedures on pharmacovigilance inspections cover at least the following processes:

a) Sharing of information;
b) Pre-authorisation inspections;
c) Co-ordination of pharmacovigilance inspections in Rwanda;
d) Preparation and planning of pharmacovigilance inspections;
e) Prioritization of pharmacovigilance inspections
f) Conduct of pharmacovigilance inspections;
g) Sign the memorandum;
h) Reporting and classification of the pharmacovigilance inspections findings
i) Communication of the findings;
j) Interaction with PSAC in relation to inspections and their follow-up;
k) Record-keeping and archiving of documents obtained or resulting from pharmacovigilance inspections;
l) Sanctions and enforcement in case of serious non-compliance; recommendations on the training and experience of inspectors performing pharmacovigilance inspections;
m) These procedures will be revised and updated as deemed necessary. New procedures may also be developed when the need is identified in relation to the inspection process.

ANNEX 10: FORMAT AND LAYOUT OF PSMF

The PSMF may be in electronic form on condition that a clearly arranged, printed copy can be made available to Rwanda FDA, 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 the content. 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:

1.0 COVER PAGE

a) The unique number assigned by the electronic system or manually to the PSMF.
b) 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).
c) The name of other concerned MAH(s) sharing the pharmacovigilance system.
d) The list of PSMFs for the MAH (concerning products with a different pharmacovigilance system).
e) The date of preparation / last update.
f) The qualified person responsible for pharmacovigilance, Annex A
g) The list of tasks that have been delegated by the QPPV, or the applicable procedural document, Annex B
h) The curriculum vitae of the QPPV and associated documents
i) Contact details
j) The lists of contracts and agreements
k) Sources of safety data, Annex C
l) Lists associated with the description of sources of safety data e.g. affiliates and third party contacts Computerized systems and Databases, Annex D, Pharmacovigilance Process, and written procedures, Annex E
m) Lists of procedural documents Pharmacovigilance System Performance, Annex F
n) Lists of performance indicators
o) Current results of performance assessment in relation to the indicators Quality System, Annex G
p) Audit schedules
q) List of audits conducted and completed audits, Annex H
r) List(s) of products covered by the pharmacovigilance system

s) Any note concerning the MAH per product Document and Record Control, Annex1
t) Logbook
u) Documentation of history of changes for Annex contents, indexed according to the Annexes A-H and their content if not provided with in the relevant annex itself.

2.0 Qualified person responsible for pharmacovigilance (QPPV)

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

a) Description of the responsibilities guaranteeing that the qualified person has sufficient authority over the pharmacovigilance system in order to promote, maintain and improve compliance;
b) A summary of curriculum vitae with the key information on the role of the qualified person responsible for pharmacovigilance, including proof of registration in Rwanda;
c) Contact details;
d) Details of back-up arrangements to apply in the absence of the qualified person responsible for pharmacovigilance;
e) A list of tasks that have been delegated by the qualified person for pharmacovigilance shall also be included in the Annexes.
f) The details provided in relation to the QPPV should also include the description of the QPPV qualifications, experience and registrations relevant to pharmacovigilance in Rwanda FDA. 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.

1.0 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 organizations and operational units relevant to the fulfillment of Pharmacovigilance obligations. This should include third parties.

The PSMF shall describe:

a) The organizational structure of the MAH(s), showing the position of the QPPV in the organization.
b) 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.

c) Diagrams may be particularly useful and the name of the department or third party should be indicated.

4.0 Outsourced activities

The PSMF, where applicable, shall contain a description of the activities and/or services subcontracted by the MAH relating to the fulfillment 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 Rwanda.

Links with other organization, 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 fulfillment of pharmacovigilance obligations should be provided. Individual contractual agreements shall be made available at the request of Rwanda FDA during inspection, audit and the list provided in the Annexes.

5.0 Sources of safety data

The description of the main units for safety data collection should include all parties responsible, for solicited and spontaneous case collection for products authorized in Rwanda. 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 Rwanda FDA 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 findings, 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 Rwanda, irrespective of indication, product presentation and 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 should be comprehensive for all studies/programmes and should include ongoing as well as completed studies/programmes in the last two years and may be located in an Annex or provided

separately.

6.0 Computerized systems and databases

The location, functionality and operational responsibility for computerized systems and databases used to receive, collect, 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 shall be 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.

7.0 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, at a regional and/or National level etc.), the nature of the data held (e.g. the type of case data retained for ICSRs) and an indication of how records are held (e.g. safety database, paper file at site of receipt) should be provided in the 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; thisshould 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 Rwanda FDA;

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 Rwanda FDA 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 procedures need not be listed, but a list may be requested as 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).

8.0 Pharmacovigilance system performance

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

i. Assessment of correctness reporting of ICSRs. In the annex, figures/ graphs should be provided to show the timeliness of reporting over the past year;
ii. Metrics used to monitor the quality of submissions and performance of pharmacovigilance. This should include information provided by Rwanda FDA regarding the quality of ICSR reporting, PSURs or other submissions;
iii. An overview of the timeliness of PSUR reporting to Rwanda FDA (the annex should reflect the latest figures used by the marketing authorization holder to assess compliance);
iv. An overview of the methods used to ensure timeliness of safety variation submissions compared to internal and Rwanda FDA regulatory deadlines, including the tracking of required safety variations that have been identified but not yet been submitted;
v. Where applicable, an overview of adherence to risk management plan commitments, or other obligations or conditions of marketing authorization(s) relevant to pharmacovigilance.
vi. Targets for the performance of the pharmacovigilance system shall be described and explained. A list of performance indicators must be provided in

ANNEX 11: PHARMACOVIGILANCE METHODS

1.0 Passive surveillance

a) Spontaneous Reports

A spontaneous report is an unsolicited communication by healthcare professionals or consumers to a company, Rwanda FDA or other organization (e.g., WHO, regional centers, poison control center) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.

Spontaneous reports play a major role in the identification of safety signals once a drug is marketed. In many instances, a company can be alerted to rare adverse events that were not detected in earlier clinical trials or other premarketing studies. Spontaneous reports can also provide important information on at-risk groups, risk factors, and clinical features of known serious adverse drug reactions. Caution should be exercised in evaluating spontaneous reports, especially when comparing drugs. The data accompanying spontaneous reports are often incomplete, and the rate at which cases are reported is dependent on many factors including the time since launch, pharmacovigilance-related activity, media attention, and the indication for use of the drug.

b. Systematic Methods for the Evaluation of Spontaneous Reports

More recently, systematic methods for the detection of safety signals from spontaneous reports have been used. Many of these techniques are still in development and their usefulness for identifying safety signals is being evaluated.

These methods include the calculation of the proportional reporting ratio, as well as the use of Bayesian and other techniques for signal detection. Data mining techniques have also been used to examine drug-drug interactions. Data mining techniques should always be used in conjunction with, and not in place of, analyses of single case reports. Data mining techniques facilitate the evaluation of spontaneous reports by using statistical methods to detect potential signals for further evaluation. This tool does not quantify the magnitude of risk, and caution should be exercised when comparing drugs. Further, when using data mining techniques, consideration should be given to the threshold established for detecting signals, since this will have implications for the sensitivity and specificity of the method (a high threshold is associated with high specificity and low sensitivity). Confounding factors that influence spontaneous adverse event reporting are not removed by data mining.
Results of data mining should be interpreted with the knowledge of the weaknesses of the spontaneous reporting system and, more specifically, the large differences in the ADR reportingrate among different drugs and the many potential biases inherent in spontaneous reporting. All signals should be evaluated recognizing the possibility of false positives. In addition, the absence of a signal does not mean that a problem does not exist.

c. Case Series

Series of case reports can provide evidence of an association between a drug and an adverse event, but they are generally more useful for generating hypotheses than for verifying an association between drug exposure and outcome. There are certain distinct adverse events known to be associated more frequently with drug therapy, such as anaphylaxis, aplastic anemia, toxic epidermal necrolysis and Stevens-Johnson Syndrome. Therefore, when events such as these are spontaneously reported, sponsors should place more emphasis on these reports for detailed and rapid follow-up.

d. Stimulated Reporting

Several methods have been used to encourage and facilitate reporting by health professionals in specific situations (e.g.in-hospital settings) for new products or for limited time periods. Such methods include on-line reporting of adverse events and systematic stimulation of reporting of adverse events based on a predesigned method. Although these methods have been shown to improve reporting, they are not devoid of the limitations of passive surveillance, especially selective reporting and incomplete information.

During the early post marketing phase, companies might actively provide health professionals with safety information, and at the same time encourage cautious use of new products and the submission of spontaneous reports when an adverse event is identified. A plan can be developed before the product is launched (e.g., through site visits by company representatives, by direct mailings or faxes, etc.). Stimulated adverse event reporting in the early post marketing phase can lead companies to notify healthcare professionals of new therapies and provide safety information early in use by the general population (e.g., Early Post-marketing Phase Vigilance). This should be regarded as a form of spontaneous event reporting; thus, data obtained from stimulated reporting cannot be used to generate accurate incidence rates, but reporting rates can be estimated.

2.0 Active surveillance

Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organized process. An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management program.
Patients with a prescription for the concerned drug may be asked to complete a consent form and give permission for later contact. A case report form (CRF) must be completed for each participant. In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than a passive reporting system.

a. Sentinel Sites

Active surveillance can be achieved by reviewing medical records or interviewing patients and/or

physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events from these sites. The selected sites can provide information, such as data from specific patient subgroups that would not be available in a passive spontaneous reporting system. Further, information on the use of a drug, such as abuse, can be targeted at selected sentinel sites. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients and increased costs. Active surveillance with sentinel sites is most efficient for those drugs used mainly in institutional settings such as hospitals, nursing homes, hemodialysiscenters, etc. Institutional settings can have a greater frequency of use for certain drug products and can provide an infrastructure for dedicated reporting. In addition, automatic detection of abnormal laboratory values from computerized laboratory reports in certain clinical setting scan provide an efficient active surveillance system. Intensive monitoring of sentinel sites can also be helpful in identifying risks among patients taking orphan drugs.

b. Drug Event Monitoring

Drug event monitoring is a method of active pharmacovigilance surveillance. In drug event monitoring, patients might be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation can be included in the questionnaire. Limitations of drug event monitoring can include poor physician and patient response rates and the unfocused nature of data collection, which can obscure important signals. In addition, maintenance of patient confidentiality might be a concern. On the other hand, more detailed information on adverse events from a large number of physicians and/or patients might be collected.

c. Registries

A registry is a list of patients presenting with the same characteristic(s). The characteristic(s) can be a disease (disease registry) or a specific exposure (drug registry). Both types of registries, which only differ by the type of patient data of interest, can collect a battery of information using standardized questionnaires in a prospective fashion. Disease registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations can help to collect data on drug exposure and other factors associated with a clinical condition. A disease registry might also be used as a base for a case-control study comparing the drug exposure of cases identified from the registry and controls selected from either patients with another condition within the registry, or patients outside the registry.

Exposure (drug) registries address populations exposed to drugs of interest (e.g., registry of rheumatoid arthritis and patients exposed to biological therapies) to determine if a drug has a special impact on this group of patients. Some exposure (drug) registries address drug exposures in specific populations, such as pregnant women. Patients can be followed over time and included

in a cohort study to collect data on adverse events using standardized questionnaires. Single cohort studies can measure incidence but without a comparison group cannot provide proof of association. However, they can be useful for signal amplification particularly for rare outcomes. This type of registry can be very valuable when examining the safety of an orphan drug indicated for a specific condition.

1.1 Comparative observational studies

Traditional epidemiological methods are a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports or case series. Major types of these designs are cross-sectional studies, case control studies and cohort studies (both retrospective and prospective).

e. Cross-sectional Study (Survey)

Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed.

These studies are best used to examine the prevalence of a disease at one-time point or to examine trends over time, when data for serial time points can be captured. These studies can also be used to examine the crude association between exposure and outcome in ecological analyses. Cross-sectional studies are best utilized when exposures do not change over time.

f. Case-control Study

In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure among the controls represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease in the two groups. Patients can be identified from an existing database or using data collected specifically for the purpose of the study of interest. If safety information is sought for special populations, the cases and controls can be stratified according to the population of interest (the elderly, children, pregnant women, etc.).

For rare adverse events, existing large population-based databases are a useful and efficient means of providing needed drug exposure and medical outcome data in a relatively short period of time. Case-control studies are particularly useful when the goal is to investigate whether there is an association between a drug (or drugs) and one specific rare adverse event, as well as to identify risk

factors for adverse events. Risk factors can include conditions such as renal and hepatic dysfunction that might modify the relationship between the drug exposure and the adverse event. Under specific conditions, a case-control study can provide the absolute incidence rate of the event. If all cases of interest (or a well-defined fraction of cases) in the catchment area are captured and the fraction of controls from the source population is known, an incidence rate can be calculated.

g. Cohort Study

In a cohort study, a population at risk for the disease (or event) is followed over time for the occurrence of the disease (or event). Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a drug at one time during follow-up, but non-exposed at another time point. Since the population exposure during follow-up is known, incidence rates can be calculated. In many cohort studies involving drug exposure, comparison cohorts of interest are selected on the basis of drug use and followed over time. Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events. Multiple adverse events can also be investigated using the same data source in a cohort study. However, it can be difficult to recruit sufficient numbers of patients who are exposed to a drug of interest (such as an orphan drug) or to study very rare outcomes.

Like case-control studies, the identification of patients for cohort studies can come from large automated databases or from data collected specifically for the study at hand. In addition, cohort studies can be used to examine safety issues in special populations (the elderly, children, patients with co-morbid conditions, pregnant women) through over-sampling of these patients or by stratifying the cohort if sufficient numbers of patientsexist.There are several automated databases available for pharmaco-epidemiological studies. They include databases that contain automated medical records or automated accounting/billing systems. Databases that are created from accounting/billing systems might be linked to pharmacy claims and medical claims databases. These datasets might include millions of patients. Since they are created for administrative or billing purposes, they might not have the detailed and accurate information needed for some research, such as validated diagnostic information or laboratory data. Although medical records can be used to ascertain and validate test results and medical diagnoses, one should be cognizant of the privacy and confidentiality regulations that apply to patient medical records.

4.0 Targeted clinical investigations

When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for, to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing can also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the drug

in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies can include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.

Sometimes, potential risks or unforeseen benefits in special populations might be identified from pre-approval clinical trials, but cannot be fully quantified due to small sample sizes or the exclusion of sub-populations of patients from these clinical studies. These populations might include the elderly, children, or patients with renal or hepatic disorder. Children, the elderly, and patients with co-morbid conditions might metabolize drugs differently than patients typically enrolled in clinical trials. Further clinical trials might be used to determine and quantify the magnitude of the risk (or benefit) in such populations.

To elucidate the benefit-risk profile of a drug outside of the formal/traditional clinical trial setting and/or to fully quantify the risk of a critical but relatively rare adverse event, a large simplified clinical trial might be conducted. Patients enrolled in a large simplified trial are usually randomized to avoid selection bias. In this type of trial, though, the event of interest will be focused to ensure a convenient and practical study is conducted. One limitation of this method is that the outcome measure might be too simplified and this might have an impact on the quality and ultimate usefulness of the trial. Large, simplified trials are also resource-intensive.

5.0 Descriptive studies

Descriptive studies are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with drug exposures. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of drugs in specified populations.

a. Natural History of Disease

The science of epidemiology originally focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest. These outcomes of interest now include a description of disease treatment patterns and adverse events. Studies that examine specific aspects of adverse events, such as the background incidence rate or risk factors for the adverse event of interest, can be used to assist in putting spontaneous reports into perspective. For example, an epidemiological study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific sub groups, such as patients with concomitant illnesses.

b. Drug Utilization Study

Drug utilization studies (DUS) describe how a drug is marketed, prescribed, and used in a

population, and how these factors influence outcomes, including clinical, social, and economic outcomes. These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics. DUS can be used to determine if a product is being used in these populations. From these studies, denominator data can be developed for use in determining rates of adverse drug reactions. DUS have been used to describe the effect of regulatory actions and media attention on the use of drugs, as well as to develop estimates of the economic burden of the cost of drugs. DUS can be used to examine the relationship between recommended and actual clinical practices.

These studies can help to determine whether a drug has the potential for drug abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of in appropriate repeat prescribing. Important limitations of these studies can include a lack of clinical outcome data or information of the indication for use of a product.

ANNEX12: DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION PLAN

DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION (DHPC)PLAN	
Medicinal product(s)/activeingredient(s)	
Marketing authorization holders	In cases where the DHPC concerns several marketing authorization holders of the same active substance or is part of a class review, the holders are strongly encouraged that a single consistent message is sent to healthcare professionals in Rwanda. All concerned marketing authorization holders in Rwanda are strongly encouraged to collaborate, so that a single DHPC is prepared and circulated in Rwanda. The letter circulated in Rwanda should cover all active substance-containing products authorized in Rwanda. It is encouraged that the marketing authorization holder in Rwanda acts as the contact point for Rwanda FDA. If no innovator product is marketed in Rwanda, it is encouraged that one of the concerned generic companies acts as contact point for Rwanda FDA.
Safety concern and purpose ofthe communication	Consider using the title of the DHPC to describe the safety concern
DHPC recipients	List all (groups of) recipients of the DHPC in this section, e.g. general practitioners, specialists, community pharmacists, hospital pharmacists, nurses, professional societies, national associations.
Partner states where the DHPC will be distributed	
Timetable Delete steps which are Date not applicable	
DHPC and communication plan agreed by Rwanda FDA	
Dissemination of DHPC	

ANNEX 13: TEMPLATE FOR DIRECT HEALTHCARE 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 Rwanda FDA 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>
Contact point
<Contact 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 Rwanda FDA>
<Additional scientific information, if applicable><List of literature references, if applicable

ANNEX 14: FORMAT OF PHARMACOVIGILANCE INSPECTION REPORT

Company Name:
PSMF:
Inspection number: [Enter inspection reference number as applicable
Date of issuance

SECTION A: ADMNISTRATIVE INFORMATION.

Inspection type:	
Name and address(es) of site(s) inspected:	
Contact person:	
Date(s) of inspection:	
Lead inspector :	
Reporting inspector	
Accompanying inspector(s) and experts:	
Previous Pharmacovigilence inspections : (Date andinspecting authority)	
Purpose of inspection:	
Products selected to provide PV system examples:	As part of the general systems review, there are products chosen for close evaluation of ADR reports, PSURs, etc.
Name and location of the qualified person for pharmacovigilance (QPPV):	Name: Contact details:
Date of first issue of report to MAH:	Date of submission
Deadline for submission of responses by MAH:	
Date(s) of receipt of responses from MAH:	
Date of final version of report:	
Report author:	Name Job title

SECTION B: GENERAL INFORMATION

1. Scope and reason for the inspection
2. Reference texts and documents for the inspection
3. Conduct inspection with summary of the organization and any significant Changes and action taken since the last inspection.

SECTION C: Inspected items

SECTION D: Findings

Definitions of inspection finding grading

1. Critical (CR):

Use the categories and subcategories listed in Appendix I followed by a short title for the finding	
<<Inspector to add text>>	
Root cause analysis	
<<MAH to add text>>	
Further assessment	
<<MAH to add text>>	
Corrective action(s)	
<<MAH to add text>>	
Deliverable(s) <<MAH to add text>>	**Due date(s)** <<MAH to add text>>
Preventative action(s)	
<<MAH to add text>>	
Deliverable(s) <<MAH to add text>>	**Due date(s)** <<MAH to add text>>
Recommendation / Observation (amend as necessary)	

MAJOR FINDINGS

Present the major findings as corresponding to the definition

Finding MA1 Use the categories and subcategories listed in Appendix I followed by a short title for the finding	
<<Inspector to add text>>	
Root cause analysis	
<<MAH to add text>>	
<<MAH to add text>>	
Corrective action(s)	
<<MAH to add text>>	
Deliverable(s) <<MAH to add text>>	Due date(s) <<MAH to add text>>
Preventative action(s)	
<<MAH to add text>>	
Deliverable(s) <<MAH to add text>>	Due date(s) <<MAH to add text>>
Recommendation / Observation (amend as necessary)	

MINOR FINDINGS

Present the minor findingsas corresponding to the definition

Marketing authorization legal basis [Tick the appropriate below.]	
	Full application
	Generic application
	Hybrid application
	Similar biological application
	Well-established use application
	Fixed combination application
	Informed consent application
	Other – Please specify:

Next PSUR submission date [if PSURs are required for the medicinal product]	DD month YYYY PSUR not required.

Recommendation / Observation (amend as necessary)

Comment:

SECTION E:

1. Evaluation by the inspectors of the response from the inspectee
2. Final conclusions and recommendations

SECTION F:

Date and signatures of lead and other inspectors, experts if applicable

ANNEX 15: STANDALONE SIGNAL NOTIFICATION FOR ACTIVE SUBSTANCE/ INN – BRAND NAME

ADMINISTRATIVE INFORMATION

Date of this notification	
Active substance(s) (invented name(s))	
Pharmaceutical form(s)/Route(s) of administration / Strength(s)	
Marketing authorization holder(s)	
QPPV	
MAH contact person for the signal	
Authorization procedure and number [Tick the appropriate box (es) below and complete as appropriate.]	
Other EAC Partner State(s) NMRA in which the MAH holds a marketing [Choose the appropriate.]☐Burundi ☐Kenya ☐Uganda ☐South Sudan ☐Tanzania ☐Zanzibar	

Marketing authorization legal basis [Tick the appropriate below.]	
	Full application
	Generic application
	Hybrid application
	Similar biological application
	Well-established use application
	Fixed combination application
	Informed consent application
	Other – Please specify:
Next PSUR submission date [if PSURs are required for the medicinal product]	DD month YYYY PSUR not required.

APPENDICES
APPENDIX I: SIGNAL DESCRIPTION

HIGHLIGHTS

Clinical relevance: (Text)

(Please briefly summarize how seriousness criteria were met in the cases, e.g. fatal, life-threatening, hospitalization etc.)

. Relevant statistical measures: (Text)

(Please provide the relevant ROR values (in particular the lower bound of the 95%confidence interval) as well as any other relevant statistical measures if applicable.

Patient exposure: (Text)

(Please provide the most recent estimate of the population cumulatively exposed to the medicinal product in the post- authorization setting and in clinical trials if applicable. Methods used to calculate the exposure do not need to be included.)

Previous awareness: (Text)

(Please provide information on any regulatory actions or previous assessments, performed at national, regional and international in relation to the signal detection. Please ensure, wherever possible, that the signal is not already addressed in other national, regional and international SPCs for the active substance.)

Additional sources other than EAC – Vigilance database:

Literature Clinical trials MAH databaseother [please specify below]

BACKGROUND (Text)

(This section should include a concise summary of the relevant information on the product(s)/ active substance (including
therapeutic indication(s)), and on the adverse reaction(s) (e.g. morbidity, epidemiology, case definition, etc.)

SIGNAL VALIDATION AND FURTHERASSESSMENT

Evidence from EAC -Vigilance
Date of the query: / /
(DD/MM/YYYY)
Monitoring periodicity (Text).....

(This section should include a summary of evidence from EAC - Vigilance, highlighting the strength of evidence, clinical relevance and a summary of the supportive cases. MedDRA terms used, number of cases, positive de-challenge or re-challenge, seriousness, dose-reaction relationship, biological and temporal plausibility, causality assessment, clinical context(e.g. drug interactions, specific population, risk factors) and quality of documentation should be provided.)

Evidence from other sources (Text)

(This section should include a summary of all additional evidence, e.g. from the MAH database, scientific literature, clinical
trials…)

CONCLUSION (Text)

(This section should include a brief statement highlighting why further analysis by the NMRAs is warranted and proposed actions.)

ANNEXES (Text)

List of literature references, if applicable
List of attachments, if applicable

APPENDIX II: WHO CAUSALITY ASSESSMENT SCALES

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) • Re-challenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable timerelationship to drug in take • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Re-challenge 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
Un-assessable/ Unclassified	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

APPENDIX III: NARANJO ALGORITHM

Naranjo algorithm for assessing the causality of an ADR

Question	Yes	No	Do not know
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse event appear after the suspected drug was administered?	+2	-1	0
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0
Are there alternative causes (other than the drug) that could solely have caused the reaction?	-1	+2	0
Was the drug detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0
Total score			

Key

Total score categories are defined as follows: ADR is: certain > 9; probable 5-8; possible 1-4; unlikely 0.

	Author	Authorized by	Approved by
Title	Division Manager of Pharmacovigilance&Food safety monitoring	Head of Food and Drugs Inspection&Safety monitoring department	Director General
Name	NTIRENGANYA Labare	ALEX GISAGARA	
Signature			
Date	01/08/2019	05/08/2019	26/08/2019