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TANZANIA FOOD AND DRUGS AUTHORITY

NATIONAL GUIDELINES FOR MONITORING MEDICINES SAFETY

(Made under Section 5 (c) of the Tanzania Food, Drugs and Cosmetics Act (Cap 219)

THIRD Edition

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TABLE OF CONTENTS

Acknowledgements 5
Abbreviations 6
Foreword 7
Introduction 8
Glossary of terms 10
1. NATIONAL MEDICINES POLICY AND LEGAL ASPECT OF PHARMACOVIGILANCE 14
2. PHARMACOVIGILANCE SYSTEMS IN TANZANIA 15
3. ROLES OF VARIOUS PARTIES 15
3.1 National Pharmacovigilance Center 15
3.2 Zonal Pharmacovigilance Centers 15
3.3 Marketing Authorization Holder (MAH)/ Manufacturers 16
3.4 Pharmacovigilance Technical Committee 17
3.5 Patients or consumers 17
3.6 Health facilities and Pharmaceutical Outlets 17
3.7 Council Health Management Team (CHMT) 18
3.8 Regional Health Management Team (RHMT) 18
3.9 TFDA zone offices 19
3.10 TFDA headquarter office 19
3.11 Development Partners 20
3.12 Public Health Programs (PHPs) 20
4. PHARMACOVIGILANCE METHODS IN TANZANIA 21
4.1 Active Surveillance 21
4.1.1 Cross-sectional study 21
4.1.2 Cross-sectional study 20
4.1.3 Case-control study 21
4.1.4 Cohort study 21
4.1.5 Targeted clinical investigation 22
4.1.6 Descriptive studies 22
4.1.7 Natural history of disease 22
4.1.8 Drug utilization study 22
4.2 Passive surveillance 23
4.2.1 Spontaneous reports 23
4.2.2 Case series of spontaneous reports 23
4.2.3 Targeted spontaneous reporting 23
4.2.4 Stimulated reporting 24
4.2.5 Literature Reports 24
4.2.7 Solicited Reports 25
5. REPORTING OF ADVERSE DRUGS REACTION 25
5.1 Spontaneous reporting 25
5.1.1 Completing the ADR reporting form 27
5.1.2 Expedited reporting requirements 28
5.1.3 Periodic Safety Update Reporting 28
5.1.4 Reporting unusual failure in efficacy 29
5.1.5 Reporting medication errors 29
5.1.6 Reporting suspected ADRs to herbal medicines 31
5.1.7 Reporting product quality defects 32
5.1.8 Patient reporting 32
5.1.9 Reporting of Overdoses 32
5.1.10 Flow of ADR information 33
5.2 Active surveillance 33
6. ASSESSMENT OF ADR REPORTS 33
6.1 Methods for causality assessment 34
6.2 Basic principles of causality assessment 34

6.3 Required data elements 34
6.4 Steps to follow during causality assessment 34
6.4.1 Thoroughly clinical, physical examination and laboratory investigation 34
6.4.3 Plausible biological or pharmacological explanation of the event 35
7. RISK COMMUNICATION STRATEGIES 36
7.1 Introduction 36
7.2 Communicating benefit-risk 36
7.3 Means of communication 36
7.4 Communicating with Media 36
7.5 A spokesperson System 36
7.6 Feedback on reported ADRs 37
8. RISK-BENEFIT ASSESSMENT BY MAH 37
8.1 Assessment of Risks 37
8.2 Assessment of Benefits 38
8.3 Improving the Risk-Benefit Balance 38
9. PHARMACOVIGILANCE INSPECTIONS 39
10. PHARMACOVIGILANCE QUALITY SYSTEMS 40
10.1 Introduction 40
10.2 Quality, quality objectives, quality requirements and quality system 40
10.2.1 Quality cycle 40
10.2.2 Overall quality objectives for pharmacovigilance 41
10.2.3 Principles for good pharmacovigilance practices 41
10.2.4 Responsibilities for the quality system within an organization 42
10.2.5 Training of personnel for Pharmacovigilance 42
10.2.6 Facilities and equipment for Pharmacovigilance 43
10.2.7 Specific quality system procedures and processes 43
10.2.7.1 Compliance management by the MAHs 43
10.2.7.2 Compliance management by the TFDA 44
10.2.7.3 Record management 44
10.2.8 Documentation of the quality system 45
10.2.9 Additional quality system documentation by MAHs 46
10.2.10 Critical pharmacovigilance processes and business continuity 46
10.2.11 Monitoring of the performance and effectiveness of the pharmacovigilance system and its quality system 47
11. SIGNAL MANAGEMENT 47
11.1 Signal 47
11.2 Signal management 48
11.3 Signal detection 49
11.4 Review of individual case safety reports 50
11.5 Statistical analyses 50
11.6 Combination of statistical methods and review of individual case safety reports 50
11.7 Signal validation 51
11.8 Signal analysis and prioritization 52
11.9 Signal assessment 53
11.10 Recommendation for action 53
11.11 Exchange of information 54
12. TRAINING AND CAPACITY BUILDING 54
13. MONITORING AND EVALUATION 54
Annex I: Adverse Drug Reaction Reporting Form(4) 56
Annex III: Key Data Elements 60
Annex V: Quality Defects Reporting Form 62
Annex VI: Patient ADR Reporting Form 64
Annex VII: Patient ADR Alert Card 68
Annex VIII: Causality Assessment Criteria for Suspected ADRs 69
Annex IX: Pharmacovigilance Indicators 72
Bibliography 97

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These guidelines have been developed to outline requirements for monitoring medicines safety in Tanzania. The second edition was developed in November, 2010 with a team of experts and contributors from a number of institutions and was revised in June 2018 to come up with the third edition. The review of guidelines was based on experiences and knowledge on pharmacovigilance activities, Pharmacovogilance Regulations, 2018, available literature and existing regional and international guidelines to include World Health Organization (WHO) and International Conference on Harmonization (ICH) guidelines (source materials are detailed in the bibliography).

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Foreword

This is third edition of the *National Guidelines for Monitoring Medicines Safety* in Tanzania which displaces the second edition entitled "National *Guidelines for Monitoring Medicines safety*". These guidelines have been made under the provisions of Section 5(c) of the Tanzania Food, Drugs and Cosmetics Act, Cap 219.

The former edition provide guidance for reporting ADRs by marketing authorization holders (MAH) and patients; It included requirements for reporting medication errors, product quality defects, overdoses and unusual lack of efficacy. The current edition has also defined requirements for all these important aspects in pharmacovigilance and also detailing roles and responsibilities of different players in this field taking into account current developments in the field of pharmacovigilance.

The document covers the collection of ADR reports for pharmaceutical products and herbal medicines. Apart from collecting information on safety of medicines, the reporting tools in these guidelines may also be used to collect safety information from use of biological products including vaccines and blood products, medical devices (e.g. dental and medical supplies, contrast media etc), and cosmetics. Adverse drug reactions for marketed products within the scope of this guidance document should be reported to TFDA and other health authorities and/or facilities as defined in these guidelines.

It should be noted that adverse events due to medicines, herbal medicines and medical devices authorized for clinical trials involving human participants pursuant to Sections 61 to 72 of the Tanzania Food, Drugs and Cosmetics Act, Cap 219 are not within the scope of these guidelines.

The guidelines allow for flexibility in approach during implementation. Alternative approaches to the principles and practices delineated in this document may be acceptable provided that they are supported by adequate justification and meet minimum recommended ADR reporting requirements. In connection to this, it is equally important to note that TFDA reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Authority to adequately assess the safety, efficacy or quality of a medicinal product.

Under-reporting of ADRs is still a challenge in the country. In view of this, TFDA will continue to create awareness and organize adequate training in collaboration with other partners. The ultimate goal is to increase the number of ADR reports received per year and henceforth enable the Authority to take the necessary regulatory actions.

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Abbreviations

ADRs	Adverse Drug Reactions
AEs	Adverse Events
ARs	Adverse Reactions
AMO	Assistant Medical Officer
BMC	Bugando Medical Center
CEM	Cohort Event Monitoring
CHMT	Council Health Management Team
CO	Clinical Officer
CRS	Catholic Relief Services
DG	Director General
EU	European Union
EPI	Expanded Programme on Immunization
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSRs	Individual Case Safety Reports
KCMC	Kilimanjaro Christian Medical Centre
MAH	Marketing Authorization Holder
MNH	Muhimbili National Hospital
MoHCDGEC	Ministry of Health, Community Development, Gender, Elderly and Children
NACP	National AIDS Control Programme
NMCP	National Malaria Control Programme
NTLP	National Tuberculosis and Leprosy Programme
OTC	Over-The-Counter
PIL	Package Information Leaflet
PHP	Public Health Programmes
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
RHMT	Regional Health Management Team
SAE	Serious Adverse Event
SUSARs	Suspected Unexpected Serious Adverse Reactions
SOPs	Standard Operating Procedures
SPC	Summary of Product Characteristics
STG	Standard Treatment Guideline
TC	Therapeutic Committee
TFDA	Tanzania Food and Drugs Authority
UMC	Uppsala Monitoring Centre
WHO	World Health Organization

Introduction

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible medicine-related problems. It is an arm of patient care and aims at getting the best outcome of treatment with medicines and other products. The science allows identification 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.

Many of the challenges in safety monitoring of medicines stem from the limited amount of information available from clinical trials at the time of authorization of a medicine. Regulators have to strike a balance between making new medicines available for use in patients as early as possible and waiting until sufficient information on a product's quality, safety and efficacy is known.

Patients in clinical trials are selected carefully and followed up very closely under controlled conditions.

After authorization, however, patients using a medicine may have other diseases and may be taking other medicines. It will also be used in a larger number of patients, raising the possibility that rare side effects could start to be seen only once the medicine is being used. Some side effects may only start to emerge once a medicine has been used for a long time.

By continuing to collect information once a medicine is available and taking action in response, regulators can continue to protect the public from emerging safety issues throughout a medicine's life cycle, thereby ensuring its safe and effective use.(6)

There are two major systems 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 health care 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) s surveillance means that active measures are taken to find adverse events.

Pharmacovigilance systems are being implemented in Tanzania since 1993. The systems are still being strengthened and coordinated by the Tanzania Food and Drugs Authority (TFDA) together with established zonal Pharmacovigilance Centers located at Kilimanjaro Christian Medical Center (KCMC) - Kilimanjaro, Muhimbili National Hospital (MNH) - Dar-es-Salaam, Bugando Medical Center (BMC) - Mwanza and Mbeya Medical Center (MMC) - Mbeya. The spontaneous reporting system has largely been used. The system uses specially designed forms (Yellow Forms) to collect adverse reaction data from patients.

Since the inception of the pharmacovigilance systems very few reports have been received by TFDA. In response to this, the TFDA has been trying to devise measures to bolster the reporting rate. Amongst the measures include engaging regional and district health systems/authorities as well as private pharmaceutical outlets in the collection of ADR reports, establishing more centers to coordinate collection of ADR reports, integrating pharmacovigilance into public health programmes, conducting

training and sensitizing health care providers, manufacturers and patients to report adverse reactions to medicines and other products.

The above measures are viewed as a cornerstone towards a successful pharmacovigilance programme and as a consequence, they have been structured and detailed in these guidelines to put context into perspective.

The guidelines therefore outline the reporting requirements among health care providers, marketing authorization holders and patients. In this respect it defines what needs to be reported, how, by who and when. It further highlights requirements for expedited reporting, reporting of product quality defects, unusual failure in efficacy, medication errors, patient reporting and reporting of overdoses.

The way reports will be assessed by TFDA, management and communication of risk as well as the roles and responsibilities of different players in pharmacovigilance have also been detailed.

In addition, the training requirements as well as monitoring and evaluation (M&E) of pharmacovigilance systems from the national level to the districts have been delineated. Various tools for collection of data including reporting forms have also been appended with the guidelines for easy referencing.

An effective use of these guidelines including the tools which have been developed will significantly improve the detection, understanding and assessment of adverse drug reactions and enable the TFDA and other stakeholders to take appropriate regulatory action and other measures respectively. Possible regulatory actions vary from continuing observation of products to cancelling the marketing authorization. Other possibilities include:

- Conducting post-marketing studies;
- Comprehensive re-assessment of the risk and benefit profile of the product;
- Product labelling changes (including addition of contraindications, warnings, precautions or supplementary ADR information in the product information;
- Alteration of the packaging to clearly identify risks and instructions on the use of the product;
- Dissemination of information to health care providers and patients about the risks;
- Issuing public alerts; or
- Withdrawing products from the market.

Glossary of terms

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

Act
The Tanzania Food, Drugs and Cosmetics Act, 2003 and all regulations relating to pharmacovigilance made under the Act.

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

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.

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.

Clinical trials
A study performed to investigate the safety of efficacy of medicines. For human medicines, these studies are carried out in human volunteers.

Cohort Event Monitoring (CEM)
A system created to actively monitor drug events in a population. Health care providers are requested to report all clinical events, regardless of whether they are suspected adverse reactions, for identified patients receiving a specified drug.

Duplication of efforts;
Is doing something more than once that doesn't need to be done more than once

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.

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).

Individual Case Safety Report (ICSR), synonym: Safety report

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.

Lack of Efficacy

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

Marketing Authorization Holder (MAH)

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

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 health care 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.

National Pharmacovigilance Centre (NPC)

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

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.

Pharmacovigilance (PV)

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

Pregnancy Exposure Registry

A prospective observational study that collects information on medicinal product exposure during pregnancy and the associated outcomes.

Periodic Safety Update Report (PSUR)

An update of the world-wide safety experience of a product obtained at defined times post marketing authorization.

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, characterise, prevent or minimise 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.

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 hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Life threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

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 hospitalisation but might jeopardise 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 hospitalisation 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.

Spontaneous reporting

An unsolicited communication of suspected adverse reactions by a health care provider or consumer to a company, TFDA or other organisation which fulfills the following three conditions:

- It describes one or more suspected adverse reactions in a patient
- The patient was given one or more medicinal products
- It does not derive from a study or any organised data collection scheme.

Summary Product Characteristics (SPC)

Product information as approved by the TFDA. The SPC serves as the basis for production of information for health care providers as well as for consumer information on labels and leaflets of medicinal products.

Toxicity

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

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 (SPC). This includes class-related reactions which are mentioned in the SPC but which are not specifically described as occurring with this product.

Vigiflow

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

1. NATIONAL MEDICINES POLICY AND LEGAL ASPECT OF PHARMACOVIGILANCE

The National Medicine Policy clearly states the need for raising awareness on reporting adverse drug reactions (ADRs) at all levels. The policy also recognizes the role of Tanzania Food and Drugs Authority (TFDA) as the leading institution in coordinating activities related to monitoring and reporting of existing and

new adverse events associated with the use of medicinal products as stipulated under Section 5 (1) (c) of the Tanzania Food, Drugs and Cosmetics Act, Cap 219. The activities include detection, assessment, understanding and prevention of ADRs. The success of this exercise necessitates cooperation among all stakeholders including health care providers, drug registrants and manufacturers in the country.

2. PHARMACOVIGILANCE SYSTEMS IN TANZANIA

There are different systems 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.). In Tanzania, both systems are being used.

There is need of establishing Pharmacovigilance Legislation in our country in which Pharmacovigilance Risk Assessment Committee will be formed that will help strengthen the safety monitoring of medicines across Tanzania. The legislation aimed to:

a. make roles and responsibilities clearer;
b. minimise duplication of effort;
c. free up resources by rationalising and simplifying reporting of periodic safety update reports;
d. (PSURs) and ADRs;
e. establish a clear legal framework for post-authorisation monitoring;
f. strengthen reporting systems for collection of high-quality data on the safety of medicines;
g. provide a more rigorous, science-based approach that integrates the concepts of benefit-risk balance and risk management planning;
h. increase engagement of patients and healthcare professionals;
i. enable provision of more and better information to the public, with greater transparency of the decision making processes.

3. ROLES OF VARIOUS PARTIES

3.1 National Pharmacovigilance Centre

There is National Pharmacovigilance Centre which is embedded with TFDA HQ Office in Dar es Salaam. The centre is under custodian of TFDA and act as the central coordination point for the Zone Pharmacovigilance**.** The National Pharmacovigilance Centre shall;

3.1.1 Develop and review ADR forms and collect reports of suspected adverse reactions to medicines and other products from the market;
3.1.2 Develop and review reporting tools;
3.1.3 Conduct causality assessment and analyze adverse reactions reports; and
3.1.4 Generate hypotheses or identify signals and communicate with the authority for action.

3.2 Zone Pharmacovigilance Centres

The Zonal Pharmacovigilance Centers located at Kilimanjaro Christian Medical Center (KCMC) - Kilimanjaro, Muhimbili National Hospital (MNH) - Dar-es-Salaam, Bugando Medical Center (BMC) – Mwanza, Mbeya Medical Center (MMC) – Mbeya, Maweni Regional Hospital- Kigoma, Dodoma Regional Hospital- Dodoma and Ligula Regional Hospital- Mtwara shall:

3.2.1 Work in collaboration with zonal TFDA offices in coordinating pharmacovigilance activities in the respective Zones;
3.2.2 Receive information, respond to queries and provide information related to pharmacovigilance to the council and regions within the respective zones;
3.2.3 Receive and distribute reporting forms to health facilities;
3.2.4 Collect reports and provide feedback to health facilities;
3.2.5 Review AR reports and feed information into the data management tool – *Vigiflow* where accessible or send them to TFDA for further action; and
3.2.6 Receive safety alerts from TFDA and share them with health care providers and patients in the respective zones.

3.3 Marketing Authorization Holder (MAH)/ Manufacturers

The Marketing Authorisation Holder (MAH)/Manufacturers should ensure that all the sections described in the Pharmacovigilance Regulations are observed. The MAH should specifically;

3.3.1 Ensure that he has an appropriate system of pharmacovigilance and risk management in place in order to assure responsibility and liability for his products on the market;
3.3.2 Employ a qualified person responsible for Pharmacovigilance with a minimum qualification of a bachelor degree such as bachelor degree of pharmacy, medicine, biostatistics or epidemiology and other field deemed acceptable by the TFDA;
3.3.3 Ensure that there is Pharmacovigilance System in place;
3.3.4 Good Pharmacovigilance Principles are observed;
3.3.5 Develop Pharmacovigilance Master File;
3.3.6 Provide information to TFDA on all adverse Drug reactions by filling in special yellow forms or electronically through electronic reporting system for ADRs;
3.3.7 Submit report on adverse reactions occurring outside Tanzania;
3.3.8 Submit a "null" six monthly report for the first two years and annually for the following three years if there is no ADR report submitted to them;
3.3.9 Inform TFDA on any significant safety issue(s) or action(s) taken by foreign agency, including the basis for such action(s), and
3.3.10 Provide periodic safety update report(s) (PSURs) for the marketed product Submit risk management plans including risk-benefit assessment reports to TFDA;
3.3.11 Monitor the outcome of measures to reduce risks to a minimum under the plan of risk management;
3.3.12 Implement a system of risk management for any medicine;
3.3.13 Have to notify the TFDA of any action to withdraw a product from the market (to suspend marketing, to withdraw from market, to request withdrawal of a market authorisation, or not to apply for a renewal of a market authorisation), together with the reason for this action no less than two months before the interruption.

3.4 Pharmacovigilance Technical Committee

To ensure effective quality pharmacovigilance system, good pharmacovigilance practice and effective monitoring and evaluation TFDA establishes pharmacovigilance technical committee. The committee comprises a team of clinicians, hospital pharmacists, nurses, radiologists, experts from medical research institute, public health experts, academicians from teaching hospitals, representative from medical association, pharmaceutical association, MAHs, pharmaceutical and biopharmaceuticals industries, clinical trial centers and consumers. The committee will convene meeting after every three months (quarterly) per year.

The committee shall be responsible for;

3.4.1 Reviewing, evaluating, and analyzing Adverse Events reports, including serious Adverse Events reports and making recommendations to the director general on appropriate regulatory actions and effective ways of communicating information on medicine safety to health care providers, MAHs, and the public;
3.4.2 Assessing pharmaceutical risks and making recommendations in this regard;
3.4.3 Making recommendations and providing advice to the director general and the MoHCDGEC on the implementation of the PV program and approaches on how to promote the safe and effective use of medicines by HCPs and the public.
3.4.4 Reviewing mechanisms for collecting ADEs and advising the director general on improvement strategies for processing them.
3.4.5 Assisting the director general to develop and implement risk minimization strategies to address drug safety concerns

3.5 Patients or consumers

Patients or consumers should report any suspected adverse reaction or event associated with the use of a medicinal product immediately to the nearest health facility, health care provider or directly to TFDA. Reporting of ADR by consumers should be done by filling in the green forms or electronically through the electronic reporting system.

3.6 Health facilities and Pharmaceutical Outlets

Health facilities should:

3.6.1 Receive and distribute ADR reporting forms to health care providers;
3.6.2 Detect, investigate, manage and report ADRs and take appropriate action to prevent ADRs;
3.6.3 Conduct preliminary identification of signals and other risk factors;
3.6.4 Communicate appropriate safety information to health management teams and the community including patients;
3.6.5 Organize and conduct staff training and sensitization on matters related to pharmacovigilance;
3.6.6 Set aside a budget for pharmacovigilance activities;

3.6.7 Identify focal person to coordinate pharmacovigilance activities within their health facilities;
3.6.8 Integrate pharmacovigilance concept into relevant committees (e.g. hospital therapeutic committees and other health committees); and
3.6.9 Maintain a register of suspected ADRs including medication errors, drug interactions etc.

Things which health facility should do to increase reporting of ADRs by health professionals

a. inclusion of pharmacovigilance agenda in the clinical meetings;
b. frequent trainings by the trained HCWs themselves, involvement of therapeutic health councils;
c. inclusion of pharmacovigilance in the supervision of health facilities, budgeting; and
d. planning of respective activities at facility level by inclusion of the activities in the Comprehensive Council Health Plan (CCHP).

3.7 Council Health Management Team (CHMT)

The Council Health Management Team (CHMT) should:

3.7.1 Appoint a District Pharmacist or any other designated person to become the focal person for pharmacovigilance activities in the respective council;
3.7.2 Supervise the implementation of pharmacovigilance activities within the council;
3.7.3 Communicate all relevant safety information to health care providers and patients in the council;
3.7.4 Conduct further investigation of signals and other risk factors;
3.7.5 Organize and conduct training and sensitization of health care providers and patients within the council;
3.7.6 Plan and budget for pharmacovigilance activities within the council; and
3.7.7 Ensure pharmacovigilance related reports are submitted to TFDA on quarterly basis; and
3.7.8 Ensure that posters and leaflets, for medical personnel such as Doctors as well as Patients are distributed.

3.8 Regional Health Management Team (RHMT)

The Regional Health Management Team (RHMT) should:

3.8.1 Appoint a Regional Pharmacist or any other designated person to become the focal person for pharmacovigilance activities in the respective region;
3.8.2 Supervise the implementation of pharmacovigilance activities within the region;
3.8.3 Receive summary report of implementation of pharmacovigilance from all districts;
3.8.4 Communicate all relevant safety information to health care providers and patients in the region;
3.8.5 Conduct further investigation of signals and other risk factors;
3.8.6 Organize and conduct training and sensitization of health care providers

and patients within the council; and

3.8.7 Provide advice to TFDA on issues pertaining to medicine's safety.

3.9 TFDA Zone Offices

The TFDA Zone Officers shall;

3.9.1 Plan and budget for pharmacovigilance activities in the respective zones;
3.9.2 Work in collaboration with zonal pharmacovigilance centers in coordinating pharmacovigilance activities in the respective zones;
3.9.3 Receive and distribute ADR forms to zonal pharmacovigilance centres and health facilities;
3.9.4 Collect, screen and enter ADR reports into *Vigiflow* where possible or send the reports directly to TFDA headquarter offices for further processing;
3.9.5 Receive safety alerts from TFDA headquarter offices and share them with zonal pharmacovigilance centers, councils, health care providers and patients;
3.9.6 Respond to queries and provide feedback information related to pharmacovigilance to the council and regions in the respective zones; and
3.9.7 Monitor and evaluate implementation of pharmacovigilance activities in the respective zones.

3.10 TFDA Headquarter Office

TFDA headquarters shall:

3.10.1 Plan and budget for national pharmacovigilance activities;
3.10.2 Develop, review and distribute ADR forms and collect reports of suspected adverse reactions to medicines and other products from the market;
3.10.3 Develop, review and distribute reporting tools;
3.10.4 Acknowledge receipt of ADR reports from health care providers, zonal pharmacovigilance centers and zonal TFDA offices;
3.10.5 Conduct causality assessment and analyze adverse reactions reports;
3.10.6 Generate hypotheses or identify signals and take appropriate regulatory action(s) based on signals generated;
3.10.7 Collect and communicate relevant safety information to all stakeholders;
3.10.8 Link with WHO program for international drug monitoring and share information on adverse reactions;
3.10.9 Provide feedback to reporters (e.g. issuing ADR Bulletins/Newsletters etc) including alerting prescribers, manufactures and the public to new risks of adverse reactions;
3.10.10 Conduct pharmacovigilance inspection at the manufacturing facilities, where relevant;
3.10.11 Monitor and evaluate all pharmacovigilance activities in the country;
3.10.12 Conduct trainings and sensitization of different stakeholders;
3.10.13 Take regulatory action on a particular medicine with serious adverse reaction;

3.10.14 Provide additional information on pharmacovigilance from other sources;
3.10.15 To upload the information into the global pharmacovigilance database (Vigiflow®).(4)
3.10.16 Carrying out inspections to ensure company pharmacovigilance systems comply with good pharmacovigilance practice.(5);
3.10.17 Each year the Authority shall make public a list of the medicinal products for which the market authorisation has been refused, revoked or suspended in the Union, whose supply has been prohibited or which have been withdrawn from the market, including the reasons for such action(6).

3.11 Development Partners

Development partners should collaborate with the Ministry of Health and Social Welfare including its institutions and other stakeholders in providing financial and technical support during implementation of pharmacovigilance activities at all levels.

3.12 Public Health Programs (PHPs)

Public health programmes (PHP) in Tanzania include; National AIDS Control Programme (NACP), National Malaria Control Programme (NMCP), National Tuberculosis and Leprosy Programme (NTLP), Immunization and Vaccine Development (IVD) Program etc. Such programmes should be actively engaged in pharmacovigilance activities. Their specific roles should include:

3.12.1 Identifying focal persons to coordinate pharmacovigilance activities;
3.12.2 Planning and budgeting for pharmacovigilance activities;
3.12.3 Collection of data using existing ADR reporting forms;
3.12.4 Distribution of ADR forms in programme sites;
3.12.5 Establishing procedures for data analysis and review;
3.12.6 Risk management and follow-up of patients;
3.12.7 Collaborating with TFDA in implementing pharmacovigilance activities;
3.12.8 Training of health care providers in reporting adverse drug reactions including other aspects of pharmacovigilance;
3.12.9 Promoting rational and safe use of medicines by health care providers, and
3.12.10 Educating and informing patients on the importance of reporting adverse drug reactions;
3.12.11 Assessment and communication of the risks and effectiveness of medicines used in the specific PHP; and
3.12.12 Setting up of an adequate email/referral system, to ease the process of ADR reporting.

3.13 Ministry of Health, Community Development, Gender, Elderly and Children (MHCDGEC)

The MoHSW shall have the following roles:

3.13.1 Develop and review policies related to pharmacovigilance activities;
3.13.2 Oversee implementation of pharmacovigilance activities, ensure effective

integration of pharmacovigilance activities within public health programs;

3.13.3 Mobilize and provide resources for pharmacovigilance activities;

3.13.4 Celebrating Pharmacovigilance Day annually; and

3.13.5 Publishing of Pharmacovigilance based articles in healthcare journals, magazines and newspapers (3).

4. PHARMACOVIGILANCE METHODS

There are mainly two types of pharmacovigilance methods in Tanzania. Active and Passive surveillance.

4.1 Active Surveillance

Active surveillance uses pharmaco-epidemiological methods to overcome the limitations of passive surveillance. Based on the signals/alerts generated by passive surveillance, it can be used to identify the focus of surveillance and apply a more rigorous and appropriate methodology to allow causality assessment of the adverse event. Its main weaknesses are its high cost and the limited number of persons it can cover. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective).

The following are different types of active surveillance;

4.1.1 Cross-sectional study

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 ecologic analyses. Cross-sectional studies are best utilized when exposures do not change over time.

4.1.2 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.

4.1.3 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 or to study very rare outcomes.

4.1.4 Targeted clinical investigation

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.

4.1.5 Descriptive studies

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

4.1.6 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 of or risk factors for the adverse event of interest can be used to assist in putting spontaneous reports into perspective. For example, an epidemiologic study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific subgroups, such as patients with concomitant illnesses.

4.1.7 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.

4.2 Passive surveillance

Passive surveillance is the most common method used in PV. It covers the entire population and monitors any adverse events that occur in patients. Although it is one of the easiest methods to implement, its weaknesses include a heavy reliance on voluntary or spontaneous reporting, which may not generate a large volume of reports on a specific product or accurate and complete reports. It also provides limited opportunity for comparisons in terms of the target and subject of the surveillance. It does, however, generate signals or alerts that active surveillance can use for further investigations.

The following are different types of passive surveillance;

4.2.1 Spontaneous reports

A spontaneous report is an unsolicited communication by healthcare professionals or consumers to a national pharmacovigilance centre, pharmaceutical company, regulatory authority or other organization (e.g., WHO, Regional Centers, Poison Control Centre) that describes one or more suspected 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 signals of drug related problems once a drug is marketed. They 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 product launch, pharmacovigilance-related regulatory activity, media attention, and the indication for use of the drug.

4.2.2 Case series of spontaneous reports

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 frequently with drug therapy, such as anaphylaxis, aplastic anaemia, toxic epidermal necrolysis and Stevens Johnson syndrome. Therefore, when events such as these are spontaneously reported, it is important that pharmacovigilance centres place emphasis on these reports for detailed and rapid follow-up.

4.2.3 Targeted spontaneous reporting

This is a variant of spontaneous reporting. It focuses on capturing adverse drug reactions in a well defined group of patients on treatment. Health professionals in charge of the patients are sensitized to report specific safety concerns. The method is intended to ensure that patients are monitored and that adverse drug reactions are reported as a normal component of routine patient monitoring and standard of care. This focused approach has the same objectives and flow of information as for spontaneous reporting. The reporting requires no active measures to look for the particular syndromes.

4.2.4 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 pre-designed case definition. Although these methods have been shown to improve reporting, they are not devoid of the limitations of spontaneous reporting, especially selective reporting and incomplete information.

4.2.5 Literature Reports

Scientific and medical literatures are a significant source of information for the monitoring of safety profile and benefit-risk balance of medicinal products, particularly in relation to the detection of new safety signals or emerging safety issues. PRHs should maintain awareness of related publications through a systematic literature review of widely used reference databases. PRHs should have procedures in place to monitor scientific and medical publications in journals, and to bring them to the attention of the PRH safety department as appropriate.

A qualified healthcare professional from the PRH should use their clinical judgment to determine the appropriate frequency of literature searches based on the active ingredient(s) of products registered under the PRH. Only ADRs which occurred in Tanzania need to be reported to the Authority, if multiple products are mentioned in the publication, the PRH should consider only those, which are identified to have causal relationship with the suspected ADR.
One report should be created for each single patient and Relevant medical information should be provided and the publication author(s) should be considered as the primary source(s).

4.2.6 Information on Suspected ADR from the Mass Media, Internet or Digital Media.

MAH should regularly screen mass media, internet or digital media for potential reports of suspected ADR. The frequency of the screening should allow potential valid ADR to be reported to the Authority within the stipulated timelines. Although not exhaustive, the following list should be considered as digital media: website, web page, blog, vlog, social network, internet forum, chat room, health portal. PRH may also consider utilising their websites to facilitate the collection of suspected ADR reports.

When collecting reports of suspected ADRs via the internet or digital media, the term “identifiable” refers to the possibility of verification of the existence of a

reporter and a patient. When one party (the Authority or PRH) is made aware that the primary source may also have reported the suspected ADR to another concerned party, the report should still be considered valid. All the relevant information necessary for the detection of the duplicate case should be included in the ADR report(s).

4.2.7 Solicited Reports

Solicited reports are defined by the ICH as those derived from organised data collection systems, which include clinical trials, registries, post-approval named-patient-use programs, other patient support and disease management programs, surveys of patients or healthcare professionals, or information gathering on efficacy or patient compliance.

New and significant safety findings presented in these articles, for which reporting is not required, should however be discussed in the relevant sections of the concerned PBRER. Their overall impact on the product benefit-risk profile should be analysed and any new safety information which may affect the benefit-risk profile of a product should be notified immediately to the Authority.

5. REPORTING OF ADVERSE DRUGS REACTION

5.1 Spontaneous reporting

When an adverse reaction to medicine is suspected, one has to complete the ADR reporting form (**Annex I & II**). Adverse drug reactions (ADRs) can also be reported electronically using the electronic reporting form which is available online at www.tfda.go.tz or can simply be reported by calling TFDA using numbers printed on the ADR form. All reports submitted will be kept CONFIDENTIAL.

a) Where to obtain and send ADR reporting forms

The ADR reporting form should be obtained, completed and sent to the following offices:

i. TFDA Headquarter offices;
ii. TFDA Zonal offices- These are located in Mwanza (for Lake Zone) Arusha (for Northern Zone), Mbeya (for Southern Highlands Zone), Mtwara (for Southern Zone), Dodoma (for Central Zone), Tabora (for Western Zone) and in Dar-es-Salaam (serving Eastern zone);
iii. Zone Pharmacovigilance centres;
iv. Regional Medical Officer's office;
v. District Medical Officer's office;
vi. In-charge of the regional and district hospitals;
vii. In-charge of the health centres;
viii. In-charge of the dispensaries;
ix. Superintendent of the community pharmacies; and
x. Superintendent of the private health facilities.

NB: The forms will be provided free of charge by TFDA and as they are already pre-

paid, reporters will not be charged for postal mailing.

b) What to report

Report all suspected reactions to pharmaceutical products, herbal medicines, biologicals (e.g. vaccines, blood products etc), medical devices (e.g. dental and medical supplies, contrast media etc) and cosmetics. The following should be reported;-

i. All ADRs as a result of prescription and non-prescription;
ii. All suspected adverse drug reactions regardless of whether or not the product was used in accordance with the product information provided by the company marketing the product;
iii. Unexpected reactions, regardless of their nature or severity, whether or not consistent with product information or labeling;
iv. An observed increase in frequency of a given reaction;
v. A serious reaction, whether expected or not;
vi. All suspected ADRs associated with drug-drug, drug-food or drug-food supplement interactions;
vii. ADRs in special field of interest such as drug abuse and drug use in pregnancy and during lactation;
viii. ADRs occurring from overdose or medication errors;
ix. Unusual lack of efficacy or when suspected quality defects are observed.
x. Product quality problems include colour change, separating of composition, caking, change of odour, questionable stability, suspected contamination, poor packaging and labeling, mislabeling, incomplete pack, defective and expired product.

c) Who should report

Submission of a report does not constitute an admission that a health care provider or the drug or the product caused or contributed to the ADR in any way as all reports are termed as suspected.

Reporters should bear in mind that any information related to the reporter and patient identities shall be kept CONFIDENTIAL.

The following should provide reports of any case of suspected ADRs when encountered by the patient:

i. Health care providers,
ii. Marketing Authorization Holders
iii. Manufacturers,
iv. Patients and the general public.

It is vital to report an ADR even if you are doubtful about the precise relationship with the given medication or you do not have all the facts. What is required is to report all SUSPECTED ADRs.

Collection of reports from several health care providers in different parts of the country assists in making associations (strengthening of signal) between a particular product and the adverse reaction. Therefore, measures should be taken to ensure that all necessary information for submission of ADR reports

are obtained and reported through the reporting forms.

d) When to report

Any suspected ADR should be reported as soon as possible. Delay in reporting will make reporting inaccurate and unreliable. Reporting while the patient is still in the health facility will give the reporter the chance to clear any ambiguity by re-questioning or re-examining the patient.

5.1.1 Completing the ADR reporting form

The ADR reporting form contains key data elements about the patient, the suspected drug, the adverse reaction, the action taken and the outcome (see **Annex III – key data elements**). Such elements enhance the quality of an ADR report. Reporters should write legibly and use a separate form for each patient. Attempts should be made to obtain as many information as provided below:

a) The patient's identity - Information about the patient's age, sex, weight, ethnicity and use of substance of abuse should be provided. The patient file number has to be stated as it is useful to get additional information when needed.

b) Information on the suspected drug - This information includes the name of the medicine, source, the dose, route of administration and the impact of withdrawal and re-administration of the suspected medicine on the adverse reaction.

i. Use brand name of suspected medicine(s). If generic name is used, specify the manufacturer of the medicine.
ii. Avoid non-standard abbreviations such as TCL (tetracycline), PCM (Paracetamol), CPZ (Chlorpromazine), etc.
iii. List any other prescription, non-prescription medicines and/or traditional medicine used concurrently with the suspected medicine with all descriptions i.e. brand name, route, dosage form, strength, frequency, indication, date started and date stopped.
iv. The dosage form such as tablet, capsule, syrup, suspension, elixir, emulsion, injection, eye drop/ointment, topical crème/ ointment, nasal drop, suppositories rectal/ vaginal etc. should be stated.
v. The strength must also be expressed in metric system, e.g. 500mg tab, 250mg/5ml syrup, 1gm rectal suppository etc. Sometimes strength can be expressed in %, e.g. 2% hydrocortisone ointment.
vi. Frequency of drug administration should be clearly notified using standard abbreviations, e.g. 3 times a day as tid or 8hrly, 2 times a day as bid or 12hrly, 4 times a day as qid or 6 hrly etc.
vii. Route of administration expressed using standard abbreviation should be used (see also **Annex IV**).
viii. The date medicine was started and discontinued (if applicable) is important data to assess the cause and effect relationship of the medicine and adverse reaction. Therefore it has to be stated clearly on the reporting form as date/ month/year. If the medicine has not been discontinued at the time of reporting, write continuing.
ix. Write the reason why the medicine was used or the diagnosis for which the medicine was prescribed for both suspected medicine and other

medicines used concurrently.

c) **Information on the adverse reaction -** A clear and brief description about the nature of adverse reaction, the date of onset, duration, time course and laboratory test results including "negative" and normal results of any relevant test performed should be reported. The severity of the reaction i.e. whether it has necessitated prolonged hospitalization or not, discontinuation of the medicine or not, etc. and the outcome of the de-challenge and re-challenge tests with the suspected medicines have to be reported.

d) **Additional information -** Any reaction the patient may have experienced previously, particularly similar to the current adverse event, either caused by the same or different medicine has to be reported. Other relevant medical history, such as allergy, chronic disease, pregnancy and other factors, which may contribute including herbal products, foods and chemicals, should be reported under this heading. You may also add here why you think the adverse effect is due to the particular medicine.

e) **Follow-up report for an ADR that has already been reported -** Any follow-up information for an ADR that has already been reported can be sent on another ADR form, or it can be communicated by telephone, fax or e-mail to TFDA indicating that it is a follow up information. The date of the original report and the report case number must be retrieved from the ADR register so that the follow up information can be matched with the original report. It is very important that follow-up reports are identified and linked to the original report.

5.1.2 Expedited reporting requirements

All serious reactions must be reported on an expedited basis using the same ADR reporting form (**Annex 1**). Expedited reports should be submitted to TFDA immediately and not later than 15 calendar days from receipt of the minimum information required for an adverse reaction report by a health care provider or personnel of the manufacturer.

Serious suspected adverse reactions occurring in all post-marketing studies of which the manufacturer is aware should be reported to the TFDA on an expedited basis.

When additional medically relevant information is received for a previously reported case, the reporting time is considered to begin again for submission of the follow-up report. In addition, a case initially classified as a non-expedited report, would qualify for expedited reporting upon receipt of follow-up information that indicates the case should be re-classified (e.g., from non serious to serious).

5.1.3 Periodic Safety Update Reporting

Periodic Safety Update Reports (PSURs) are important pharmacovigilance documents. They provide an opportunity for Marketing Authorization Holders (MAHs) to review the safety profile of their products and ensure that the Summary of Product Characteristics (SPC) and Package Leaflets are up to date. They also provide a valuable source of pharmacovigilance data.

MAHs should submit PSURs to TFDA. PSURs should as a minimum contain the following information:

i. Information on the product (i.e. brand name, dosage form, strength, manufacturer and country of origin),
ii. The scope of drug safety data and the surveillance period,
iii. Collection of adverse drug reaction (ADR) information (i.e. local serious ADRs, local non-serious ADRs, foreign serious ADRs, foreign non-serious ADRs, case reports published on international or local literatures including academic conferences).

5.1.4 Reporting unusual failure in efficacy

Reports of unusual failure in efficacy must be reported to TFDA using ADR reporting form (**Annex 1**). The underlying principle is that if a product fails to exert the expected intended effect, there may be an adverse outcome for the patient, including an exacerbation of the condition for which the product is being used.

Possible reasons for lack of efficacy include:

i. Did not retain the medication because of vomiting or severe diarrhea;
ii. Lack of adherence to treatment schedule;
iii. Inadequate dose;
iv. Poor quality medication;
v. Counterfeit medication;
vi. Incorrect diagnosis;
vii. Interactions reducing blood levels; and
viii. Drug resistance.

Clinical judgment should be exercised by the health care provider to determine if the problem reported is related to the product itself, rather than one of treatment selection or disease progression since products cannot be expected to be effective in 100% of the patients. One example of unusual failure in efficacy is a previously well-stabilized condition that deteriorates when the patient changes to a different brand or receives a new prescription.

Lack of efficacy of medicines used for the treatment of life-threatening diseases, vaccines and contraceptives should be considered as requiring **expedited reporting**.

5.1.5 Reporting medication errors

Medication errors are any patient safety incident (PSIs) where there has been an error in the process of prescribing, preparing, dispensing, and administering, monitoring or providing advice on medicines.

These PSIs can be divided into two categories; errors of Commission or errors of omission. The former include, for example, wrong medicine or wrong dose. The latter include, for example, omitted dose or a failure to monitor, such as international normalised ratio for anticoagulant therapy.

TFDA should ask for Yellow Cards for all suspected ADRs to medicines and vaccines under additional monitoring (marked with an inverted black triangle symbol (▼). Reports of all serious ADRs are requested for established medicines and vaccines. Serious reactions include those that are: fatal;

i. Life-threatening;
ii. Disabling;
iii. incapacitating;
iv. result in congenital abnormalities; and
v. result in or prolong hospitalisation.

They should be reported even if the effect is well recognised.

TFDA should also particularly be interested in receiving, through the Yellow Card Scheme, reports of suspected ADRs:

i. In children;
ii. In patients that are over 65;
iii. To biological medicines;
iv. associated with delayed drug effects and interactions; and
v. Complimentary therapies such as homeopathic and herbal remedies.

Causality does not have to be proved in order to report a suspected ADR, a suspicion is enough.

a. By health care providers

Medication errors can occur when prescribing, repacking, dispensing, or administering a product. Common causes of medication errors include poor communication, patient misunderstanding, and ambiguities in product names or directions for use.

Errors, or hazardous conditions including administering the wrong drug, strength, or dose of medications; confusion over look-alike/sound-alike medicines; incorrect route of administration; calculation or preparation errors; misuse of medical equipment; and errors in prescribing, transcribing, dispensing, and monitoring of medications should be reported to TFDA using the ADR reporting form (**Annex 1**).

Medication errors reporters are encouraged to submit associated materials such as product photographs, containers, labels, prescription order scans, etc, that would support the information being submitted. TFDA guarantees CONFIDENTIALITY of information received and respects reporters' wishes as to the level of detail included in the report.

When reporting errors, include the following:

i. Describe the error or preventable adverse medicine reaction. What went wrong?

ii. Was this an actual medication error (reached the patient) or are you expressing concern about a potential error or writing about an error that was discovered before it reached the patient?
iii. Patient outcome.
iv. Type of health facility (hospital, dispensary, retail pharmacy, ADDO, drug outlets, health centers, home-based services, etc).
v. The generic name (INN or official name) of all products involved.
vi. The brand name of all products involved.
vii. The dosage form, concentration or strength, etc.
viii. How was the error discovered/intercepted?
ix. State your recommendations for error prevention.

Medication incidence should include

i. Date of incident. Incident should be reported not more than four weeks after the incident;
ii. Medicine name;
iii. Proprietary name;
iv. Manufacturer;
v. Use of the term 'other' in the medication process field. Options include: prescribing/preparation/dispensing, administration, monitoring etc
vi. Use of the term 'other' in type of medication error. Options include: wrong patient, medicine, route, dose frequency, quantity, omitted etc
vii. Staff type reporting the incident. Options include doctor, nurse, pharmacist etc
viii. Review of free text description of what happened, death or severe harm reports.
ix. Actions taken to prevent recurrence;
x. Apparent causes; and
xi. Clinical outcome codes indicating death or severe harm(7).

NB. Do not submit any patient identifiable information when reporting medication errors.

b. By Marketing Authorization Holders

The Marketing Authorization Holders or product registrants should report cases of medication errors that are associated with serious adverse reactions on an expedited basis. Cases not associated with adverse reactions and near misses should only be reported in Periodic Safety Update Reports (PSURs). Cumulative information on medication errors, resulting in adverse reaction or not, should be discussed in the section of the PSUR on the overall safety evaluation. The potential for medication errors and their prevention should be addressed in the Risk Management Plan.

5.1.6 Reporting suspected ADRs to herbal **medicines**

Health professionals, providers of herbal medicines, patients/consumers and manufacturers should report any suspected adverse reactions to herbal medicines. Details of the suspected herbal product to include species name and/or brand name or ingredients, country of origin, batch number, expiry date and name of provider should be provided. The precise Latin binomial botanical name (genus, species, author as well as name of family) of the medicinal plants concerned should be used whenever possible together with the plant parts used and extraction and preparation methods employed. Suspected adverse reaction to herbal medicines should be reported using ADR reporting form (**Annex 1**).

5.1.7 Reporting product quality defects

Medicines quality concerns include a number of hazards, which may be due to improper formulation, packaging, or labelling. Some product quality defects may occasionally pose a threat. Problems of quality defect that occur during the manufacturing, shipping, or storage of prescription or over-the-counter products shall be reported to the Marketing Authorization Holder and direct to TFDA using the form for reporting poor quality products **(Annex V).**

On receipt of the report of medicine quality defect that are associated with serious adverse reactions, MAH should assess the situation and take immediate action within reasonable time. Simultaneously, MAH should report such product quality defects and measures taken to TFDA in writing within 15 calendar days after becoming aware of the defect.

5.1.8 Patient reporting

A simplified reporting form (**Annex VI**) should be used by patients to report information on suspected adverse drug reactions. Patients should be 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 (i.e. **Patient ADR Alert Card** appended as **Annex VII**) by the health care provider who diagnosed and managed the reaction. The Alert Card will be prepared and distributed to health facilities by TFDA.

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.

5.1.9 Reporting of Overdoses

The health care provider should report cases of overdose (accidental or intentional) that lead to suspected serious adverse reactions on an expedited basis. This should include reports that indicate that the taking of the suspected drug led to suicidal intention and a subsequent overdose of the suspected drug or other medications.

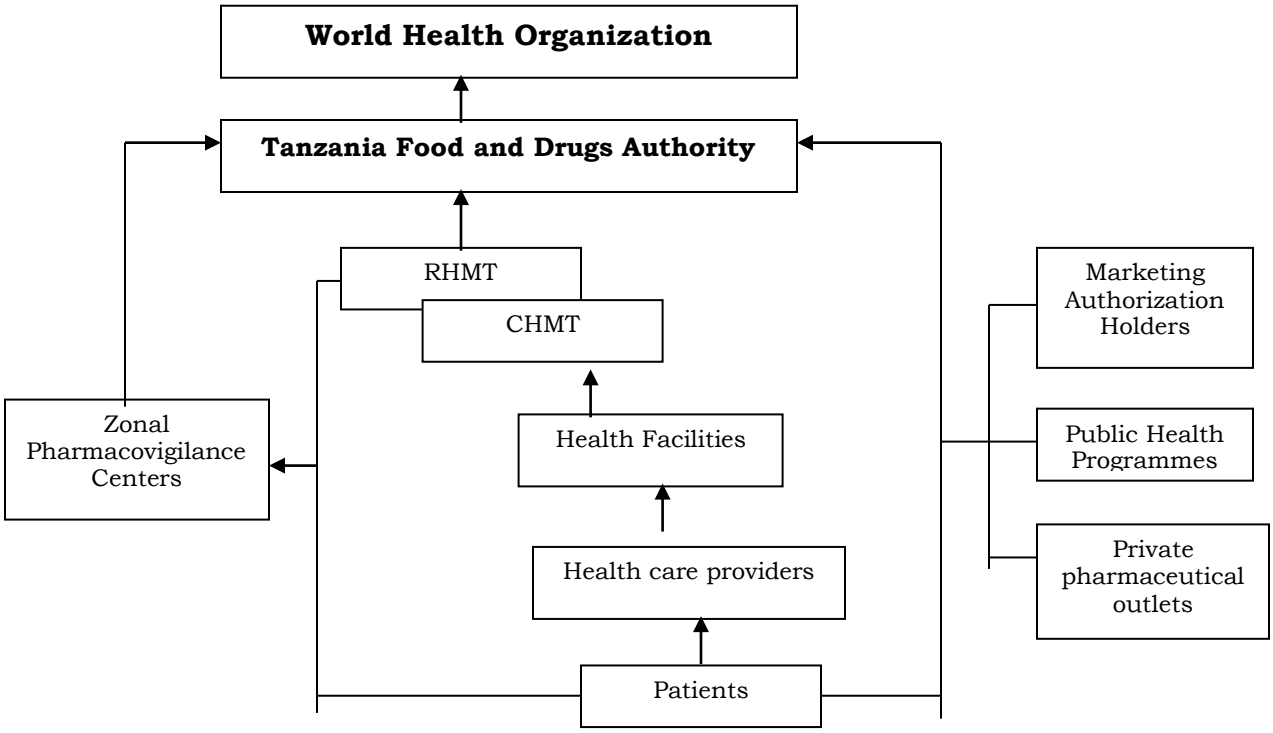
Reports of overdose with no associated adverse reactions should not be reported as adverse reactions. They should be routinely followed up by the health care providers to ensure that information is as complete as possible with regard to early symptoms, treatment and outcome of an overdose.

Patients are encouraged to immediately report to health care providers in case of over dosage.

5.1.10 Flow of ADR information

The flow of ADR information is summarized in Fig. 1 below.

Fig.1: Flow of ADR information



5.2 Active surveillance

Various approaches of active surveillance exist, including cohort event monitoring (CEM), case-control studies, registries, drug utilization studies etc. Such studies may be conducted for the purpose of identifying previously unrecognized safety concerns (hypothesis-generation), investigating potential and identified risks (hypothesis-testing in order to substantiate a causal association), or confirming the known safety profile of a medicinal product under normal conditions of use. They may also be conducted to quantify established adverse reactions and to identify risk factors.

Data collection tools to be used in active surveillance studies may be designed or adapted depending on the disease or medicines under investigation.

Reports on active surveillance studies should be submitted to TFDA for evaluation and appropriate regulatory action where applicable.

6. Assessment of ADR reports

Assessment of ADR reports (i.e. individual case safety reports (ICSRs)) should be carried out to determine the seriousness and expectedness of the suspected

adverse reaction(s). Reaction(s) to new medical entities and unexpected or serious reactions should receive priority.

6.1 Methods for causality assessment

Several methods are available, but the WHO and Naranjo methods are the most commonly used. Causality assessment methods differ in many respects but share certain common features. Causality assessment may be done on single case reports as well as on case series. The World Health Organization (WHO) causality assessment criteria (**Annex VIII**) together with the World Health Organization - Adverse Reaction Terminologies (MedDRA) should be used for signal detection. When a signal is identified, the possibility of a causal relationship should be established and in these circumstances, all relevant adverse reaction data should be further analyzed. All ICSRs fulfilling the minimum information requirements should be included in the overall analysis. Additional information may be requested from manufacturer or reporter if needed.

6.2 Basic principles of causality assessment

Causality assessment in PV involves making a decision based on information regarding the temporal relationship between a drug exposure and the occurrence of a suspected ADR. Decisions on causality are also based on examining the extrinsic (i.e. data supporting involvement or otherwise of the drug) and intrinsic (i.e., data about the disease or patient) imputability. Thus, the following elements are typically evaluated during causality assessment: drug, patient, event, chronology, and re-challenge/de-challenge.

6.3 Required data elements

For a report to be considered valid, four minimum data elements are required: an identifiable patient, a suspected medicine, an event, and an identifiable reporter. However, good quality adverse event reports containing more than the minimum required data elements will facilitate proper assessment of causality.

6.4 Steps to follow during causality assessment

The steps stipulated herein should act as guide during establishment of drug-event causal association. Always try to describe the reaction as clearly as possible and where possible provide an accurate diagnosis.

6.4.1 Thoroughly clinical, physical examination and laboratory investigation

a) Take a Proper History and do a proper examination
   i. A full drug and medical history should be done to determine possible causes of the event. For instance factor like patient's underlying disease, other drug/s, over-the-counter medicines or traditional medicines; toxins or foods should be taken into consideration; and
   ii. A drug-related cause should be considered, especially when other causes do not explain the patient's condition.
b) Temporal spatial association or time relationship between the use of the suspected drugs and the occurrence of the event

i. Some reactions occur immediately after being given a medicine while other reactions take time to develop; and
ii. The time from the start of therapy to the time of onset of the suspected reaction must be logical.

c) Physical examination and laboratory investigation
i. Few drug produce distinctive physical signs which can be easily detected;
ii. Exceptions include fixed drug eruptions, steroid-induced dermal atrophy, acute extrapyramidal reactions; and
iii. Lab tests are especially important if the drug is considered essential in improving patient care or of the lab test results will improve management of the patient e.g. Antiretroviral therapy regimen containing Tenofovir which may pause difficult to stop immediately when there is suspected deterioration of renal function.

6.4.2 Effect of de-challenge and re-challenge on occurrence of the event should be determine (when necessary)

6.4.2.1 Dechallenge = withdraw of drug
a. Resolution of suspected ADR when the drug is withdrawn is a strong, although not conclusive indication of drug-induced disease.

6.4.2.1 Rechallenge = reintroducing the drug after a dechallenge.
a. This is only justifiable when the benefit of re-introducing the drug to the patient outweighs the risk of recurrence of the reaction.
b. This is rare. In some cases the reaction may be more severe on repeat exposure.

6.4.3 Plausible biological or pharmacological explanation of the event

6.4.3.1 Is the reaction known to occur with the particular drug as stated in the package insert or other reference? This involves supportive evidence from leaflets, similar case findings reports, published reputable research on the matter; and

6.4.3.2 If the reaction is not documented in the package insert, it does not mean that the reaction cannot occur with that particular medicine.

The TFDA together with other parties, where applicable, should carry out the assessment. Data on adverse reactions should also be shared with the WHO through the data management tool – Vigiflow.

7. RISK COMMUNICATION STRATEGIES

7.1 Introduction

Effective communication of risk for TFDA and stakeholders is vital. Communicating the risks of medicines in an accurate and understandable way is hard enough, but for informed decision making it is essential that risks be communicated in the context of benefits.

7.2 Communicating benefit-risk

Good communication describe the risks of medicines in the context of their benefits to allow for informed decisions on treatment and contributing to its aim of safe and appropriate medicines use.

Good benefit-risk communication can be considered as being material that is:

a. of good quality – that is, evidence-based, clear and accurate.
b. unbiased and independent
c. timely and up-to-date – as well as
d. regular and predictable release of information
e. adapted to the target audience

Post-authorisation communication includes updates of medicines information to reflect new indications or contra-indications or other variations to the marketing authorisation, as well as communication on emerging safety issues, e.g. stage-by-stage communication on safety referrals.

7.3 Means of communication

Communication about risk can be provided through different means such as;

a. Website
b. Newsletters
c. Print media like Drug Safety Bulleting
d. Social media

7.4 Communicating with Media

The media is an important gateway to inform the public and shapes their view and attitude towards medicines. In the long term, building a partnership with the media is the key to keep the public regularly informed about the safety of medicines.

7.5 A spokesperson System

Spokespersons will vary depending on the level where communication will be provided as per government protocols. At district level, the District Medical Officer will be responsible; the Regional Medical Officers will be responsible for the regional level while the Director General of TFDA will be responsible at National Level. The DMO and RMO shall liaise with TFDA before communicating anything to media.

7.6 Feedback on reported ADRs

Adverse reaction reports sent to TFDA and other parties should be acknowledged after receipt. Acknowledgement letters should be sent within one (1) week, where possible. This will motivate and encourage reporters to keep sending reports and as a result improve the reporting rate.

Signals generated by running queries on Vigiflow should be communicated to health care providers and all other stakeholders.

Results from the literature scan, statistics and regulatory measures taken should be communicated to health care providers and other stakeholders through the TFDA - Drug Safety Newsletter, TFDA website (www.tfda.or.tz), press releases, media and all other possible means.

In order for the TFDA to evaluate and investigate ADRs there is a minimum of four pieces of information needed. These are:

a. an identifiable patient from information on, for example, age and gender;
b. an identifiable reporter (typically the organisation);
c. a suspected medicine (brand/generic name or active ingredient); and
d. a suspected reaction.

8. RISK-BENEFIT ASSESSMENT BY MAH

MAH should submit risk management plan(s) and immediately notify the TFDA of any change in the balance of risks and benefits of their products.

Overall risk-benefit assessment should take into account and balance all the benefits and risks. Risk-benefit assessment should be conducted separately in the context of each indication and population, which may impact on the conclusions and actions.

Whenever possible, both risks and benefits should be considered in absolute terms and in comparison to alternative treatments. The magnitude of risk that may be considered acceptable is dependent on the seriousness of disease being treated and on the efficacy of the medicinal product. The populations being treated must also be taken into account.

8.1 Assessment of Risks

Assessment of risks involves a stepwise process requiring identification, confirmation, characterization (including identification of risk factors), and quantification of the risk in the exposed population. Overall assessment of risks should consider all available sources of information, including:

8.1.1 Spontaneous adverse reaction reports;
8.1.2 Adverse reaction data from studies which may or may not be company-sponsored;
8.1.3 In-vitro and in-vivo laboratory experiments;
8.1.4 Epidemiological data;
8.1.5 Registries, for example of congenital anomalies/birth defects;
8.1.6 Data published in the scientific literature;

8.1.7 Investigations on product quality; and
8.1.8 Data on sales and product usage.

Important issues, which should be addressed in the assessment of adverse reactions, include evidence of causal association, seriousness, absolute and relative frequency and presence of risk factors, which may allow preventive measures. The quality and degree of evidence of risks should be taken into account.

In the assessment of risks and consideration of regulatory action, it is important to note that rarely even a single case report may establish a causal association with the suspected medicinal product and impact on the risk-benefit balance. Risk assessment should also take account of the potential for overdose, misuse, abuse, off-label use and medication errors.

When new safety concerns are identified, which, could have an impact on the overall risk-benefit balance of a medicinal product, the MAH should propose appropriate studies to further investigate the nature and frequency of the adverse reactions. A new or updated Risk Management Plan should be proposed accordingly.

8.2 Assessment of Benefits

When a new or changing risk is identified, it is important to re-evaluate the benefit of the medicinal product using all available data. The benefit of a medicinal product can be seen as the decrease in disease burden associated with its use. Benefit is composed of many parameters including: the extent to which the medicinal product cures or improves the underlying condition or relieves the symptoms; the response rate and duration and quality of life.

In the case of prophylactic medicinal products, the benefit may be considered as the reduction of the expected severity or incidence of the disease. With diagnostics, the benefit will be defined in terms of sensitivity and specificity or, in other words, false negative and false positive rates.

Any available information on misuse of the product and on the level of compliance in clinical practice, which may have an impact on the evaluation of its benefits, should also be considered. The quality and degree of the evidence of benefit should be taken into account. Benefit should, as far as possible, be expressed in quantitative terms in a way that makes it comparable to the risks.

8.3 Improving the Risk-Benefit Balance

The MAH should aim to optimize the safe use and the risk-benefit balance of an individual product and ensure that the adverse effects of a medicinal product do not exceed the benefits within the population treated. The risk-benefit balance of a medicinal product cannot be considered in isolation but should be compared with those of other treatments for the same disease.

The risk-benefit balance may be improved either by increasing the benefits (e.g. by restricting use to identified responders), or by reducing the risks using risk minimising measures (e.g. by contraindicating the use in patients particularly at risk, reducing dosage, introducing precautions of use and warnings and, if

appropriate, pre-treatment tests to identify patients at risk, monitoring during treatment for early diagnosis of adverse reactions).

When proposing measures to improve the risk-benefit balance of a product, their feasibility in normal conditions of use should be taken into account. If dose reduction is considered as a method of risk minimization, the impact of dose reduction on efficacy should be carefully evaluated.

If there are important new safety concerns requiring urgent action, the MAH, should initiate urgent safety restrictions. These measures should be immediately communicated to TFDA. The following types of actions may be necessary and may be initiated by the MAH:

a. Variation of marketing authorization(s) in respect of the indication, dosing recommendations, contraindications, warnings and precautions for use or information about adverse reactions or other sections of the Summary of Product Characteristics (SPC) and the Package Information Leaflet (PIL);
b. Direct provision of important safety information to health care providers, patients and the general public;
c. Withdrawal of the product from the market.

9. PHARMACOVIGILANCE INSPECTIONS

The MAH should establish pharmacovigilance systems.
Such systems will be inspected by TFDA to ensure compliance with pharmacovigilance requirements. Inspections will be routine as well as targeted to MAHs suspected of being non-compliant. The reports 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 focus of inspections will be to determine that the MAH has personnel, systems and facilities in place to meet their regulatory obligations.

These inspections will be prioritized based on the potential risk to public health, the nature of the products, extent of use, number of products that the MAH has on the market and other risk factors.

Where an inspection reveals non-compliances the MAH will be required to prepare a remedial action plan to correct the non-compliances and avoid their recurrence.

The MAH may be required to provide reports and where necessary evidence of the progress and completion of the action plan. There may be re-inspection at an appropriate time to verify the progress and success of these remedial actions.

In addition, in the event of non-compliance, regulatory actions may be taken by TFDA which might include the following:

a. Education and facilitation – MAHs may be informed of non-compliance and advised on how this can be remedied,

b. Re-inspection - Non-compliant MAHs may be re-inspected to ensure compliance is achieved,
c. Warning - A formal warning letter may be issued to remind MAHs of their pharmacovigilance regulatory obligations,
d. Naming non-compliant MAHs - TFDA will make public a list of MAHs found to be seriously or persistently non-compliant,
e. Urgent safety restriction,
f. Variation, suspension or revocation of the Marketing Authorization in accordance with the Tanzania Food, Drugs and Cosmetics Act, Cap 219.

10. PHARMACOVIGILANCE QUALITY SYSTEMS

10.1 Introduction

This chapter contains guidance for the establishment and maintenance of quality assured pharmacovigilance systems for marketing authorization holders and other stakeholders. How the systems of these organizations interact while undertaking specific pharmacovigilance processes is described in each respective chapter of this guideline.

Pharmacovigilance quality system is used by the MAH, other stakeholders and by TFDA to fulfill the tasks and responsibilities listed in this guideline and designed to monitor the safety of authorized products and detect any change to their risk-benefit balance. The TFDA likewise maintains a pharmacovigilance system to fulfill its pharmacovigilance activities.

For performing their pharmacovigilance activities, TFDA and stakeholders should establish and use quality systems that are adequate and effective.

10.2 Quality, quality objectives, quality requirements and quality system

For the purpose of good pharmacovigilance practice, which provides guidance on structures and processes of a pharmacovigilance system, the quality of a pharmacovigilance system can be defined as all the characteristics of the system which are considered to produce, according to estimated likelihoods, outcomes relevant to the objectives of pharmacovigilance. In general terms, quality is a matter of degree and can be measured. Measuring if the required degree of quality has been achieved necessitates pre-defined quality requirements. Quality requirements are those characteristics of a system that are likely to produce the desired outcome, or quality objectives.

The quality system is part of the pharmacovigilance system and consists of its own structures and processes. It should cover organizational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system as well as appropriate resource management, compliance management and record management.

10.2.1 Quality cycle

The quality system should be based on all of the following activities:

10.2.1.1 Quality planning: establishing structures and planning integrated and consistent processes;

10.2.1.2 Quality adherence: carrying out tasks and responsibilities in accordance with quality requirements;
10.2.1.3 Quality control and assurance: monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out; and
10.2.1.4 Quality improvements: correcting and improving the structures and processes where necessary.

10.2.2 Overall quality objectives for pharmacovigilance

The overall quality objectives of a pharmacovigilance system are:

10.2.2.1 Complying with the legal requirements for pharmacovigilance tasks and responsibilities;
10.2.2.2 Preventing harm from adverse reactions in humans arising from the use of authorized medicinal products within or outside the terms of marketing authorization or from occupational exposure;
10.2.2.3 Promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare providers and the public; and
10.2.2.4 Contributing to the protection of patients' and public health.

10.2.3 Principles for good pharmacovigilance practices

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

10.2.3.1 The needs of patients, healthcare providers and the public in relation to the safety of medicines should be met;
10.2.3.2 Upper management should provide leadership in the implementation of the quality system and motivation for all staff members in relation to the quality objectives;
10.2.3.3 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;
10.2.3.4 All persons involved with the entire organization should engage in continuous quality improvement following the quality cycle;
10.2.3.5 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;
10.2.3.6 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;
10.2.3.7 Good cooperation should be fostered between TFDA and MAHs, public health organizations, patients, healthcare providers, learned societies and other relevant bodies in accordance with the applicable legal provisions.

10.2.4 Responsibilities for the quality system within an organization

A sufficient number of competent and appropriately qualified and trained personnel with minimum qualification of bachelor degree of pharmacy, medicine, biostatistics or epidemiology should be available for the performance of pharmacovigilance activities. Their responsibility should include adherence to the principles.

For the purpose of a systematic approach towards quality in accordance with the quality cycle; managerial staff (i.e. staff with management responsibilities) in any organization should be responsible for:

10.2.4.1 Ensuring that the organization documents the quality system;
10.2.4.2 Ensuring that the documents describing the quality system are subject to document control in relation to their creation, revision, approval and implementation;
10.2.4.3 Ensuring that adequate resources are available and that training is provided;
10.2.4.4 Ensuring that suitable and sufficient premises, facilities and equipment are available;
10.2.4.5 Ensuring adequate compliance management;
10.2.4.6 Ensuring adequate record management;
10.2.4.7 Reviewing the pharmacovigilance system including its quality system at regular intervals in risk- based manner to verify its effectiveness and introducing corrective and preventive measures where necessary;
10.2.4.8 Ensuring that mechanisms exist for timely and effective communication, including escalation processes of safety concerns relating to medicinal products within an organization;
10.2.4.9 Identifying and investigating concerns arising within an organization regarding suspected non-adherence to the requirements of the quality and pharmacovigilance systems and taking corrective, preventive and escalation action as necessary;
10.2.4.10 Ensuring that audits are performed.

In relation to the management responsibilities described above, upper management within an organization should provide leadership through:

a. Motivating all staff members, based on shared values, trust and freedom to speak and act with responsibility and through recognition of staff members' contributions within the organization; and
b. Assigning roles, responsibilities and authorities to staff members according to their competencies and communicating and implementing these throughout the organization.

10.2.5 Training of personnel for Pharmacovigilance

Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes by an organization is intrinsically linked with the availability of a sufficient number of competent and appropriately qualified and trained personnel. All personnel involved in the performance of pharmacovigilance activities should receive initial and continued training. For MAHs and other stakeholders, this training should relate to the roles and responsibilities of the personnel.

The MAH/manufacturers and any responsible organization should keep training plans and records for documenting, maintaining and developing the competences of personnel. Training plans should be based on training needs assessment and should be subject to monitoring.

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

There should be a process in place within the organization to check that training results in the appropriate levels of understanding and conduct of pharmacovigilance activities for the assigned tasks and responsibilities, or to identify unmet training needs, in line with professional development plans agreed for the organizations as well as the individual staff members.

Adequate training should also be considered by the organization for those staff members to whom no specific pharmacovigilance tasks and responsibilities have been assigned but whose activities may have an impact on the pharmacovigilance system or the conduct of pharmacovigilance. Such activities include but are not limited to those related to clinical trials, technical product complaints, medical information, terminologies, sales and marketing, regulatory affairs, legal affairs and audits. Appropriate instructions on the processes to be used in case of urgency, including business continuity, should be provided by the organization to their personnel.

10.2.6 Facilities and equipment for Pharmacovigilance

Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes is also intrinsically linked with appropriate infrastructure to support the processes. Infrastructure should include office space, information technology (IT) systems and (electronic) storage space. They should be located, designed, constructed, adapted and maintained to suit their intended purpose in line with the quality objectives for pharmacovigilance, also be sustainable. Infrastructures which are critical for the conduct of pharmacovigilance should be subject to appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose. There should be processes in place to keep awareness of the valid terminologies in their valid versions and to keep the IT systems up-to-date accordingly.

10.2.7 Specific quality system procedures and processes

10.2.7.1 Compliance management by the MAHs

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

a. The continuous monitoring of pharmacovigilance data, the examination of options for risk minimization and prevention and that appropriate measures are taken by the MAHs;
b. The scientific evaluation of all information on the risks of medicinal products as regards patients' or public health, in particular as regards adverse reactions in human beings arising from use of the product within or outside the terms of its marketing authorization or associated with occupational exposure;
c. The submission of accurate and verifiable data on serious and non-serious adverse reactions to the TFDA within the legally required time-limits;
d. The 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. Effective communication by the MAH with the TFDA, including communication on new or changed risks, the pharmacovigilance system master file, risk management systems, risk minimizations measures, periodic safety update reports, corrective and preventive actions and post-authorization safety studies (PASS);
f. The update of product information by the MAH in the light of scientific knowledge;
g. Appropriate communication of relevant safety information to healthcare providers and patients/consumers.

10.2.7.2 Compliance management by the TFDA

For the purpose of compliance management, the TFDA should establish specific quality system procedures and processes in order to achieve all of the following objectives:
a. Ensuring the evaluation of the quality, including completeness, of pharmacovigilance data submitted;
b. Ensuring the assessment of pharmacovigilance data and its processing in accordance with the legal timelines;
c. Ensuring independence in the performance of pharmacovigilance activities;
d. Ensuring effective communication with patients, healthcare providers, MAHs and the general public;
e. Conducting inspections, including pre-authorization inspections.

Independence in the performance of pharmacovigilance activities is interpreted in the sense that all regulatory decisions on medicinal products should be taken in the sole interest of patients' and public health.

10.2.7.3 Record management

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

A record management system should be put in place for all documents used for pharmacovigilance activities, ensuring their retrievability as well as traceability of the measures taken to investigate safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process.

The record management system should support:

a. The management of the quality of pharmacovigilance data, including their completeness, accuracy and integrity;
b. Timely access to all records;
c. Effective internal and external communication; and
d. The retention of documents relating to the pharmacovigilance systems and the conduct of pharmacovigilance for individual medicinal products, in accordance with the applicable retention periods.

In this context, it should be ensured that the fundamental right to personal data protection is fully and effectively guaranteed in all pharmacovigilance activities in conformity with legal provisions. The purpose of safeguarding public health constitutes a substantial public interest and consequently the processing of personal data should be justified if identifiable personal data are processed only where necessary and only where the parties involved assess this necessity at every stage of the pharmacovigilance process. As part of a record management system, specific measures should therefore be taken at each stage in the storage and processing of pharmacovigilance data to ensure data security and confidentiality. This should involve strict limitation of access to documents and to databases to authorized personnel respecting the medical and administrative confidentiality of the data.
There should be appropriate structures and processes in place to ensure that pharmacovigilance data and records are protected from destruction during the applicable record retention period. The record management system should be described in a record management policy.

10.2.8 Documentation of the quality system

All elements, requirements and provisions adopted for the quality system should be documented in a systematic and orderly manner in the form of written policies and procedures, such as quality plans, quality manuals and quality records.
A quality plan documents the setting of quality objectives and sets out the processes to be implemented to achieve them. A procedure is a specified way to carry out a process and may take the format of a standard operating procedure and other work instruction or quality manual. A quality manual documents the scope of the quality system, the processes of the quality system and the interaction between the two. A quality record is a document stating results achieved or providing evidence of activities performed.

In order to have a systematic approach, the MAH/manufacturers should define in advance:
a. Quality objectives specific to their organizations in accordance with the overall quality objective and the structure- and process-specific quality objectives in accordance with each chapter of good pharmacovigilance practice; and
b. Methods for monitoring the effectiveness of the pharmacovigilance system.

The quality system should be documented by:

i. Documents on organizational structures and assignments of tasks to personnel;

ii. Training plans and records;
iii. Instructions for the compliance management processes;
iv. Appropriate instructions on the processes to be used in case of urgency, including business continuity
v. Performance indicators where they are used to continuously monitor the good performance of pharmacovigilance activities
vi. Reports of quality audits and follow-up audits, including their dates and results.

Training plans and records should be kept and made available for audit and inspection. It is recommended that the documentation of the quality system also includes:

i. The methods of monitoring the efficient operation of the quality system and, in particular, its ability to fulfill the quality objectives;
ii. A record management policy;
iii. Records created as a result of pharmacovigilance processes which demonstrate that key steps for the defined procedures have been taken;
iv. Records and reports relating to the facilities and equipment including functionality checks, qualification and validation activities which demonstrate that all steps required by the applicable requirements, protocols and procedures have been taken;
v. Records to demonstrate that deficiencies and deviations from the established quality system are monitored, that corrective and preventive actions have been taken, that solutions have been applied to deviations or deficiencies and that the effectiveness of the actions taken has been verified.

10.2.9 Additional quality system documentation by MAHs

In addition to the quality system documentation, MAHs should document:
i. Their human resource management in the pharmacovigilance system master file (PSMF)
ii. Job descriptions defining the duties of the managerial and supervisory staff.
iii. An organizational chart defining the hierarchical relationships of managerial and supervisory staff
iv. Instructions on critical processes in the pharmacovigilance system master file (PSMF); and
v. Their record management system in the pharmacovigilance system master files (PSMF).

It is recommended that the documentation of the quality system additionally includes the organizational structures and assignments of tasks, responsibilities and authorities to all personnel directly involved in pharmacovigilance tasks.

10.2.10 Critical pharmacovigilance processes and business continuity

The following pharmacovigilance processes should be considered as critical include:

i. Continuous safety profile monitoring and benefit-risk evaluation of authorized medicinal products;
ii. Establishing, assessing and implementing risk management systems and evaluating the effectiveness of risk minimization;

iii. Collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of individual case safety reports (ICSRs) from any source;
iv. Signal management;
v. Scheduling, preparation (including data evaluation and quality control), submission and assessment of periodic safety update reports;
vi. Meeting commitments and responding to requests from the TFDA, including provision of correct and complete information;
vii. Interaction between the pharmacovigilance and product quality defect systems;
viii. Communication about safety concerns between MAHs and the TFDA, in particular notifying changes to the risk-benefit balance of medicinal products;
ix. 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;
x. Keeping product information up-to-date with the current scientific knowledge, including the conclusions of the assessment and recommendations from the TFDA;
xi. Implementation of variations to marketing authorizations for safety reasons according to the urgency required.

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

i. Provisions for events that could severely impact on the organization's staff and infrastructure in general or on the structures and processes for pharmacovigilance in particular; and
ii. Back-up systems for urgent exchange of information within an organization, amongst organizations sharing pharmacovigilance tasks as well as between marketing authorization holders and the TFDA.

10.2.11 Monitoring of the performance and effectiveness of the pharmacovigilance system and its quality system

Processes to monitor the performance and effectiveness of a pharmacovigilance system and its quality system should include:
a. Reviews of the systems by those responsible for management;
b. Audits;
c. Compliance monitoring;
d. Inspections;
e. Evaluating the effectiveness of actions taken with medicinal products for the purpose of minimizing risks and supporting their safe and effective use in patients.

11. SIGNAL MANAGEMENT

11.1 Signal

This is the reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or known but incompletely documented previously based on the context of frequency of

occurrence and degree of seriousness. 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. A signal does not imply causation. It can provide preliminary information only for postulating a hypothesis and not for testing it.

11.2 Signal management

The 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, literature information or other data sources, there are new risks associated with a drug and related products or whether known risks have changed. The signal management process concerns all stakeholders involved in the safety monitoring of drug, vaccine, medical devices including patients, healthcare professionals, MAHs, TFDA and scientific committees. Whereas the ADRs database will be a major source of pharmacovigilance information, the signal management process covers signals arising from any source, only signals related to an adverse reaction shall be considered.

The objective of signal management in this guideline is to provide general guidance and requirements on structures and processes involved, to describe how these structures and processes are applied in Tanzania.

The signal management process has the following steps;

i. Signal detection
ii. Signal validation
iii. Signal analysis & prioritization
iv. Signal assessment
v. Recommendation of action
vi. Exchange of information

Although these steps generally follow a logical sequence, the wide range of sources of information available for signal detection may require some flexibility in the conduct of signal management e.g.

i. When signal detection is primarily based on a review of individual case safety reports (ICSRs), this activity may include validation and preliminary prioritization of any detected signal;
ii. When a signal is detected from results of a study, it is generally not possible or practical to assess each individual case, and validation may require collection of additional data;
iii. Recommendation for action (followed by decision in accordance with the applicable legislation) and exchange of information are components to be considered at every step of the process.

For the purpose of these guidelines, signals originating from the monitoring of data from spontaneous reporting systems are considered as the starting point of the signal management process. The same principles should apply for data originating from other sources. The sources of information are diverse and may include quality, clinical and non-clinical trials, systematic reviews and meta-analyses; pharmacovigilance and pharmacoepidemiological data. Specific sources for signals include spontaneous adverse drug reaction (ADR) reporting

systems, active surveillance systems, non-interventional studies, clinical trials, scientific literature and other sources of information.

Signals from spontaneous reports may be detected from monitoring of individual case safety reports (ICSRs), ADR databases, articles from the scientific literature or review of information provided by marketing authorization holders in the context of regulatory procedures (e.g. variations, renewals, post-authorization commitments, periodic safety update reports (PSURs), Risk Management Plan (RMP) updates or from other activities related to the on-going benefit-risk monitoring of a products. Other sources of spontaneous report may be poison centers, vaccine surveillance programmes, reporting systems established by marketing authorization holders, and any other structured and organized data collection schemes allowing patients and healthcare professionals to report suspected adverse reactions related to the products.

TFDA will liaise with other institutions or organizations managing such reporting system so as to be informed of these suspected adverse reactions. Suspected serious ADRs should be confirmed if possible through other data sources such as ―National Pharmacovigilance and Safety reports database‖ if accessible to MAHs and ―Vigibase of Uppsala Monitoring Centre ''UMC'' (accessible for only member medicines authorities but not for MAHs).

11.3 Signal detection

The detection and clinical assessment of signals is an important domain of PV. Analysis of the TFDA pharmacovigilance database can be used for signal detection to be reviewed by the PTC to determine any conclusions and make decisions on that report. Various recognized methods are used to detect signals depending on the type of drug or related product it is intended to cover.

The detection of signals is based on a multidisciplinary approach. Signal detection within TFDA or MAH-specific ADRs database shall be complemented by statistical analysis where appropriate. In order to determine the supporting evidence of a signal a recognized methodology has to be applied taking into account the clinical relevance, quantitative strength of the association, the consistency of the data, the exposure-response relationship, the biological plausibility, experimental findings, possible analogies and the nature and quality of the data.

Detailed guidance on methods of signal detection may be found in the Report of CIOMS Working group VIII Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS, Geneva 2010). Whichever methods are employed for the detection of signals, the same principles should apply, namely:

i. The method used should be appropriate for the data set; for example, the use of complex statistical tools may not be appropriate for smaller data sets;
ii. Data from all appropriate sources should be considered;
iii. Systems should be in place to ensure the quality of the signal detection activity.
iv. Any outputs from a review of cumulative data should be assessed by an appropriately qualified person in a timely manner.

v. The process should be adequately documented, including the rationale for the method and periodicity of the signal detection activity.

Detection of signals may be performed based on a review of ICSRs, from statistical analyses in large databases, or from a combination of both.

11.4 Review of individual case safety reports

ICSRs may originate from a spontaneous reporting system, post- authorization studies and monitoring of literature. Even a single report of a serious or severe adverse reaction (for example, one case of toxic epidermal necrolysis, aplastic anaemia or liver transplant, or serious adverse event concerning children or pregnancy) may be sufficient to raise a signal and to take further action.

11.5 Statistical analyses

Signal detection is now increasingly based on a regular periodic monitoring of large databases of reports of ADRs. Such databases allow generation of statistical reports presenting information on adverse reactions received over a defined time period for a given drug, vaccine or medical devices. Various methods have been developed to identify statistics of disproportionate reporting, i.e. higher reporting than expected for suspected adverse reaction for a give drug of interest compared to all other drug in the database (expressed e.g. as a lower bound of the proportionate reporting ratio >1).

Given the limitations of these methods, statistics of disproportionate reporting alone do not necessarily indicate that there is a signal to be further investigated or that a causal association is present. Use of statistical tools may not be appropriate in all situations. The size of the data set, the completeness of the available information and the severity of the adverse reaction(s) should be taken into account when considering the use of statistical methods and the selection of criteria for the detection of signals. The periodicity at which statistical reports should be generated and reviewed may vary according to the drug or vaccine or medical devices its indication and any known potential or identified risks. Some products may also be subject to an increased frequency of data monitoring. The duration for this increased frequency of monitoring may also vary and be flexible with the accumulation of knowledge of the risk profile associated with the use of the concerned drug or vaccine or medical devices.

However, a review of signals generated with this methodology must be analyzed by clinicians and drug safety experts before a conclusion can be reached. Each method used for signal detection has its advantages and disadvantages, and no one method can be considered the gold standard. The PTC of the TFDA identifies and reviews signals from the national database.

11.6 Combination of statistical methods and review of individual case safety reports

Statistical reports may be designed to provide tools for identifying suspected adverse reactions that meet pre-defined criteria of frequency, severity, clinical importance, novelty or statistical association. Such filtering tools may facilitate the selection of ICSRs to be reviewed as a first step. The thresholds used in this filtering process (for example, at least 3 cases reported) may vary according to

the extent of usage of the drug and thus the potential public health impact. Irrespective of the statistical method used, where statistical reports are used to automate the screening of a database, signal detection should always involve clinical judgments and the corresponding ICSRs should be individually reviewed, considering their clinical relevance. The statistical method should therefore be a supporting tool in the whole process of signal detection and subsequent validation.

11.7 Signal validation

Signal validation is 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. To validate a signal the following should be taken into account:

a) Clinical relevance including, for example:
   i. strength of evidence for a causal effect (e.g. number of reports, exposure, temporal association, plausible mechanism, de/re-challenge, alternative explanation/confounders);
   ii. seriousness and severity of the reaction and its outcome;
   iii. novelty of the reaction (e.g. new and serious adverse reactions);
   iv. drug-drug interactions;
   v. Reactions occurring in special populations

b) Previous awareness: - the extent to which information is already included in the summary of product characteristics or patient leaflet; - whether the association has already been assessed in a PSUR or was discussed at the level of a scientific committee or has been subject to a regulatory procedure. In principle only a new signal for which there is no previous awareness should be validated. However, an already known association may give rise to a new signal if its apparent frequency of reporting, its duration, its severity or a change in the previously reported outcome (such as new fatality) suggests new information as compared with the information included in the summary of product characteristics or previously assessed by the competent authority. Availability of other relevant sources of information providing a richer set of data on the same association:
   i. literature findings regarding similar cases;
   ii. experimental findings or biological mechanisms;
   iii. Screening of databases with larger datasets (e.g. TFDA safety reports database when the signal was sourced initially by data from MAH specific database (if accessible to MAH), and UMC Vigibase when the signal was sourced initially from TFDA safety reports database).

The magnitude and clinical significance of a signal may also be examined by descriptive analyses in other available data sources or by analysis of the characteristics of exposed patients and their drug or any related products utilization patterns. Signals for which the validity is not confirmed may deserve special attention in subsequent analyses i.e. it may be appropriate to continue to monitor the potential signal until there is enough evidence to confirm the signal. For example, there might be an inadequate case documentation or a supporting evidence of a causal association only in some of the ICSRs. In such scenarios, new cases of the same adverse reaction or follow-up reports of

previously received cases should be reviewed at appropriate time intervals to ensure that all relevant cases are considered. MAH and TFDA should establish tracking systems to capture the outcome of the validation of signals including the reasons why signals were not validated as well as information that would facilitate further retrieval of ICSRs and validation of signals.

11.8 Signal analysis and prioritization

A key element of the signal management process is to promptly identify validated signals with important public health impact or that may significantly affect the benefit-risk profile of the medicinal product in treated patients.

These signals require urgent attention and need to be prioritized for further management without delay. This prioritization process should consider:

a. The impact on patients depending on the severity, reversibility, potential for prevention and clinical outcome of the association;
b. The consequences of treatment discontinuation on the disease and the availability of other therapeutic options;
c. The strength and consistency of the evidence supporting an association, e.g., biological plausibility, a high number of cases reported in a short period of time, the measure of disproportionality of reporting and rapid increase of that measure over time and identification of the signal in different settings (e.g. general practice and hospital settings), data sources or countries;
d. Clinical context (e.g. whether the association suggest a clinical syndrome that may include other reactions);
e. The public health impact, including the extent of utilization of the product in the general population and in special populations (e.g. pregnant women, children or the elderly) and the patterns of medicinal product utilization (e.g. off-label use or misuse). The public health impact may include an estimation of the number of patients that may be affected by an adverse reaction and this number could be considered in relation to the size of the general population, the population with the target disease and the treated population;
f. Increased frequency or severity of a known adverse reaction;
g. Novelty of the suspected adverse reaction, e.g. when an unknown suspected adverse reaction occurs shortly after the marketing of a new medicinal product;
h. If a marketing authorization application for a new active substance is still under evaluation.

In some circumstances, priority can also be given to signals identified for drugs and related products or events with potential high media and pharmacovigilance stakeholder interest in order to communicate the result to the public and healthcare professionals as early as possible. The outcome of signal prioritization should include a recommendation of the time frame for the management of the signal. The outcome of the signal prioritization process should be entered in the tracking system, with the justification for the priority attributed.

11.9 Signal assessment

The objective of signal assessment is to further evaluate a validated signal so as to identify the need for additional data collection or for any regulatory action. It consists of an assessment of the available pharmacological, non-clinical and clinical data and information from other sources. This review should be as complete as possible regarding the sources of information, including the application dossier, literature articles, spontaneous reports, expert consultation, and information held by MAH and competent authorities.

When information is drawn from a range of sources, the strengths and limitations of each source should be considered in order to assess the contribution they can provide to the overall evaluation of the signal in terms of a recommendation for action. Summarizing information from different data sources also requires the choice of an internationally agreed case definition (e.g. Brighton collaboration case definition for vaccines). If no such definition exists, an operational definition should be developed. Signals may need to be assessed at a broader level e.g. at the therapeutic or system organ class level.

The search for information to assess the significance of a signal may also need to be extended to other products of the class and to other adverse reactions, such as to other terms linked to a complex disease (e.g. optic neuritis as a possible early sign of multiple sclerosis), to a prior stage of a reaction (e.g. QT prolongation and torsades de pointes) or to clinical complications of the adverse reaction of interest (e.g. dehydration and acute renal failure). Gathering information from various sources may take time. For a new signal of a serious or severe adverse reaction, measures should be taken at any stage in the management of a signal including detection, if the information already available supports the conclusion that there is a potential risk that needs to be prevented or minimized in a timely manner.

11.10 Recommendation for action

Signal assessment results in a recommendation that either no further action is required at this point in time or a further action is needed. Although the recommendation for action normally takes place in a logical sequence after signal assessment based on the extent of the information, the need for action should be considered throughout the signal management process. For example, the first case of an adverse reaction indicating a manufacturing defect may require immediate recall of a product batch. The review of available information at the signal validation or signal prioritization stages may similarly conclude that the evidence is sufficiently strong to introduce temporary measures. In such situations, it is still necessary to proceed with a formal assessment of the signal to confirm or not the safety issue in order to extend or lift the temporary measures.

The recommendation for action may include a request for:

a. Immediate measures including the possibility of suspending the marketing authorization of the medicinal product;
b. additional information to be provided by the marketing authorization holder, e.g. in order to confirm if a conclusion is valid for all indications and patient groups;

c. Periodic review of the signal, for example through PSURs;
d. Additional investigations or risk minimization activities;
e. An update of the product information through a regulatory procedure;
f. Conduct of a post-authorization safety study.

Whenever actions are requested of the MAH, the request should specify a timeframe by which they should be completed, including provision of progress reports and interim results, proportionate to the severity and public health impact of the signal.

11.11 Exchange of information

Information on validated signals, Emerging Safety Issues and the outcome of signal assessments should be exchanged between TFDA and MAH. Marketing authorization holders should communicate signals that may have implications for public health and the benefit-risk profile of a product immediately to TFDA as an Emerging Safety Issue based on authority requirements, and when appropriate this should include proposals for action. The outcomes of signal assessment involving new or changed risks and risks that have an impact on the benefit-risk balance of the concerned drug or any related product should be communicated to the public including health care professionals and patients as well as to the concerned MAH.

12. TRAINING AND CAPACITY BUILDING

Training and capacity building in pharmacovigilance are required for health care providers working at all health facilities to detect, understand, assess and prevent adverse drug reactions. Health care providers therefore need to be made aware that ADR monitoring is a part of good professional practice.

Training and capacity building are required to ensure that health care providers understand prescribing practices for medicines, the correct dosage regimens and how treatment failures are defined. In conjunction, they need to be taught the reaction profile of the medicines used, how to identify ADRs, how to manage them, when to refer patients, the basic data elements required in an ADR report, how to report, to whom and when.

Common concerns and barriers to reporting by health care providers will need to be addressed during training activities. Communication issues also need to be addressed in training courses. Health care providers in peripheral health facilities in rural and remote areas should also be included in training schemes.

The training manual developed by TFDA should be used during training. The MoHSW should also incorporate pharmacovigilance concept in the training curricula of health training institutions.

13. MONITORING AND EVALUATION

The TFDA, RHMT, CHMT, health facilities and PHPs should respectively establish a monitoring and evaluation (M&E) system to periodically monitor and

evaluate the performance of the pharmacovigilance system. The M&E system should essentially evaluate whether, or to what extent:

a. The reporting is complete, timely and accurate;
b. Response has been quick enough;
c. Case management has been appropriate; and
d. Action has been appropriate to avoid system error.

A set of indicators (**Annex 8**) should be used when evaluating the pharmacovigilance system. The indicators amongst other things will evaluate the following:

a. Distribution of reporting by health care provider category, specialization or patient reporting;
b. Reporting quality, e.g. completeness of information, precision of description, contributory value to decision-making;
c. Proportion of reports, describing reactions that are serious or previously unknown;
d. Promptness of reporting;
e. Reporting rate, e.g. the number of case reports per unit of population or number of health care providers; and
f. Evaluation of the impact of adverse reactions on morbidity, mortality and health care costs (often done by analysing hospital admissions due to ADRs).

ANNEX I:

TFDA Tanzania Food & Drugs Authority	**ADVERSE DRUG REACTION REPORTING FORM**	***TFDA/DMC/CTP/F/012*** ***Rev #:0***

REPORT OF SUSPECTED ADVERSE REACTION TO MEDICINES OR VACCINES

Note: Identities of reporter, patient and institution will remain confidential

I. PARTICULARS OF PATIENT	
Patient Initials or Record No.: - _____	Sex: - Male ❑ Female ❑
Date of Birth (dd-mm-yyyy) or age:- _____	Weight in kg:- _____

II. DETAILS OF ADVERSE REACTION	
Description of reaction: ……. ……. ……. ……. ……. ……. …….	Date Reaction Started →___/___/____ Date Reaction Stopped (if known) → ___/___/____ Onset latency……

Health related information: Medical history (e.g. hepatic, renal, HIV), allergies, pregnancy, smoking, alcohol use, etc. ***Please write any relevant medical and laboratory results including dates (if done)*** ……
……
……
……

III. DETAILS OF SUSPECTED MEDICINE/VACCINE USED							
Name of suspected medicine(s)/ vaccine(s) (Specify brand name or manufacturer if known).	**Dosage**	**Frequency**	**Route**	**Therapy Date**		**Batch. No & Expiry date (If known)**	**Reason for use**
				Start	**Stop**		
1.							
2.							
3.							
Other medicines used at the same time and or one month before (including herbal medicines)							
1.							
2.							
3.							

IV. MANAGEMENT OF ADVERSE REACTION		
Reaction subsided after stopping the suspected drug/reducing the dose:	❑ Yes	❑ No ❑Unknown
Reaction reappeared after reintroducing drug:	❑ Yes	❑ No ❑ Not applicable
Seriousness of the Reaction **(please tick all that apply):**		
❑ Discomfort but able to work	❑ Caused persistent disability or incapacity	
❑ Discomfort could not work	❑ Caused a congenital anomaly	
❑ Required or prolonged hospitalization	❑ Patient Died	
❑ Life threatening	❑ Others, please give details……	
Treatment of adverse reaction	❑ No	❑ Yes **(if yes please specify)**:…… …… ……
Outcome of the reaction	Not yet recovered ❑	Recovered (Date):___ /____/ ____ ❑ Died (Date):___/__/ Unknown ❑

Cause of death …… ……

V. THERAPEUTIC FAILURE
PLEASE WRITE IF THE MEDICINE(S)/VACCINE(S) SHOWED LACK OF EFFICACY BELOW : (Continue at the back)
VI. MEDICATION ERRORS AND OVERDOSAGE
PLEASE WRITE DETAILS OF MEDICATION ERRORS AND OVERDOSAGE BELOW:
PLEASE WRITE ANY OTHER RELEVANT ADDITIONAL INFORMATION BELOW :

VII. PARTICULARS OF REPORTER /HEALTH CARE PROVIDER		
Name: _____ _____	Profession:	Name and Address of the health facility: _____

Contact phone No: _____ E-mail: ___
_____ _____
_____

Signature: _____ Date of this _____
report: ____ / ____/_____

❑ *Please tick if you wish to receive information about other local reports associated with the suspected drug(s)*

Thank you for your cooperation	***Submission of an ADR case report does not discredit the competence of the reporter.***	***Ref No. (for official use)***

First Fold

Guide to filling the form

How to report?

- Dully fill in the form as required
- Use a separate form for each patient
- Report direct to TFDA through the following addresses:-

Mail : Tanzania Food and Drugs Authority,
P. O. Box 77150, Dar es Salaam

Fax:: 22- 2450793

Phone: 22-2450512 / 2450751

Internet; http://www.tfda.or.tz
E-mail: adr@tfda.or.tz

The ADR reporting form and the guidelines are also available for downloading at http://www.tfda.or.tz

An Adverse Drug Reaction (ADR) is defined as a reaction which is noxious and unintended, and which occurs at doses normally used in human for prophylaxis, diagnosis, or therapy of a disease, or for the modification of physiological function.

What to report?

Please report all undesirable patient effect suspected to be associated with drugs, cosmetics or medical devices use.

Report even if:

- You're not sure that the product caused the event
- You don't have all the details

When to report?

As soon as possible

Submission of follow-up reports:

Any follow-up information for an ADR that has already been reported can be sent on another ADR form or it can be communicated directly to TFDA by telephone, fax or e-mail. Please indicate that it is a follow-up report.. It is very important that follow-up reports are identified and linked to the original report.

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DAR ES SALAAM

Annex II: Key Data Elements

Some data elements might not be relevant, depending on the circumstances. Attempts should be made to obtain follow-up information on as many other listed items as are applicable to the case.

1. Patient Details

- Initials
- Other relevant identifier (patient number, for example)
- Gender
- Age, age category (e.g., adolescent, adult, elderly), or date of birth
- Concomitant or Pre-existing conditions
- Medical history
- Relevant family history

2. Suspected Medicinal Product(s)

- Brand name as reported
- Common Name, e.g., International Nonproprietary Name (INN)
- For herbal products, it is important to include the Latin binomial, author reference, family, type of extract (e.g., aqueous versus alcoholic, including percent of solvent), part of the plant used, ingredients and quantity of each (for combination products - the suspected ingredient)
- Batch/lot number
- Indication(s) for which suspect medicinal product was prescribed or tested
- Dosage form and strength
- Daily dose (specify units, e.g., mg, ml, mg/kg) and regimen
- Route of administration
- Starting date and time
- Stopping date and time, and duration of treatment

3. Other Treatment(s)

The same information as in item 2 should be provided for the following:

- Concomitant medicinal products (including non-prescription, OTC products, herbal products, complementary and alternative therapies, etc.)
- Relevant medical devices and cosmetics

4. Details of Adverse Drug Reaction(s)

- Full description of reaction(s), including body site and severity
- The criterion (or criteria) for regarding the report as serious if reported as such
- Description of the reported signs and symptoms
- Specific diagnosis for the reaction
- Onset date (and time) of reaction
- Stop date (and time) or duration of reaction
- Dechallenge and rechallenge information
- Relevant diagnostic test results and laboratory data
- Setting (e.g., hospital, health center, dispensary)
- Outcome (recovery and any sequelae)
- For a fatal outcome, stated cause of death
- Relevant autopsy or post-mortem findings
- Relatedness of product to reaction(s)/event(s)

5. Details of Reporter of an Adverse Reaction

- Name
- Mailing address
- Electronic mail address
- Telephone and/or facsimile number
- Reporter type (consumer, health care professional, etc.)
- Profession (specialty)

6. Administrative and Market Authorization Holder Details

- Source of report (e.g., spontaneous, literature etc)
- Date the event report was first received by MAH
- Country in which the reaction occurred
- Type (initial or follow-up) and sequence (first, second, etc.) of case information reported to TFDA
- Name and address of MAH
- Name, address, electronic mail address, telephone number, and facsimile number of contact person of MAH
- MAH's identification number for the case (the same number should be used for the initial and follow-up reports on the same case)

Annex III: Route of Administration – Standard Abbreviations

ROUTE	**CODE**
Buccal	BU
Conjuctival	CO
Dental	DE
Implant	MP
Inhalation	IH
Insufflation	IS
Intra-arterial	IA
Intra-articular	IR

Intra-cardiac	IC
Intradermal	ID
Intramuscular	IM
Intranasal	IN
Intraperitoneal	IP
Intrapleural	IL
Intrathecal	IT
Intratracheal	TR
Intrauterine	IU
Intravenous	IV
Intravesical	IB
Per oral	PO
Per rectal	PR
Subcutaneous	SC
Sublingual	SL
Systemic (if route is not Specified)	SY
Topical (external)	TO
Transmammary transfer	TM
Urethral	UR
Vaginal	VA

ANNEX IV:

TFDA Tanzania Food & Drugs Authority	**QUALITY DEFECTS REPORTING FORM**	***TFDA/DMC/CTP/F/013 Rev #:0***

FORM FOR REPORTING POOR QUALITY PRODUCTS

Note: Identities of reporter(s) will remain confidential

PRODUCT IDENTITY	
Brand Name:…… Generic Name:…… Batch/Lot Number:…… Date of Manufacture:…… Expiry Date:…… Country of Origin:……	Name and Address of Distributor/Supplier: …… …… …… …… …… …… ……
PRODUCT FORMULATION (Tick appropriate box)	**COMPLAINT (Tick appropriate box(es))**
❑ Tablets/Capsules	❑ Colour change
❑ Oral Suspension/Syrup	❑ Turbid Solution
❑ Injection	❑ Change of Odour
❑ Cream/Ointment/Liniment/Paste	❑ Caking
❑ Powder for reconstitution of suspension	❑ Moulding
❑ Powder for reconstitution of injection	❑ Separating
❑ Eye drops	❑ Powdering/Crumbling
❑ Ear drops	❑ Incomplete Pack
❑ Nebulizer solution	❑ Mislabeling
❑ Diluent	❑ Other, please specify:
❑ Other, please specify:	
Describe the complaint in detail:	

STORAGE CONDITIONS			
Does the product require refrigeration?	❑ Yes	❑ No	Other details

			(if necessary)
Was the product available at the facility?	❑ Yes	❑ No	
Was the product dispensed and returned by client?	❑ Yes	❑ No	
Was the product stored according to manufacturer's recommendations?	❑ Yes	❑ No	
Comments (if any)			

REPORTER NAME AND CONTACT ADDRESS

Name of Reporter: Contact Address:

Contact Phone No:

_____

E-mail: (if available)

_____

Date of this report:

_____

Thank you for your cooperation	***Ref No. (for official use)***

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Phone: 22-2450512 / 2450751

Internet; http://www.tfda.or.tz
E-mail: adr@tfda.or.tz

The poor quality reporting form and guidelines are also available for downloading at http://www.tfda.or.tz

What to report?

Please report all product defects suspected to be associated with drugs, vaccines, cosmetics or medical devices use.

When to report?

As soon as possible

MAH should report product quality defects and measures taken to TFDA in writing within 15 calendar days after becoming aware of the defect.

.

Moisten gum and fold. For maximum adhesion, press down for few seconds

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ANNEX V:

TFDA Tanzania Food & Drugs Authority	**PATIENT ADR REPORTING FORM**	***TFDA/DMC/CTP/F/014 Rev #:0***

ADVERSE REACTION PATIENTS' REPORTING FORM

(For reporting adverse reactions and product problems by non-health care providers)

Note: Identities of patient will remain confidential

I. PERSON REPORTING	
Patient ❑ Community health worker ❑ Mother ❑ Relative ❑ Other ❑ Specify: _____ Name of the health facility the medicine was obtained from: _____	Sex: - Male ❑ Female ❑ Age of the patient_____

II. BRIEF DESCRIPTION OF THE REACTION/EVENT	
……. ……. ……. ……. ……. ……. ……. …….	Date Reaction Started →__/__/__ Date Reaction Stopped (if known) →__/__/__ Date reported……

III. DETAILS OF SUSPECTED MEDICINE USED					
Name of suspected medicine(s)	**Dosage**	**Frequency**	**Route**	**Therapy Date**	
				Start	**Stop**
1.					
2.					
3.					

IV. DESCRIPTION OF ANY HERBAL MEDICINE THE PATIENT WAS TAKING

V. SERIOUSNESS OF THE ADVERSE REACTION	
❑ Discomfort but able to	❑ Caused persistent disability or incapacity

work	
❑ Discomfort could not work	❑ Caused a congenital anomaly
❑ Required or prolonged hospitalization	❑ Patient Died: Date of death _____
❑ Life threatening	❑ Others, please give details……

VI. SOURCE OF THE MEDICINE	
❑ Hospital Pharmacy	❑ Traditional Healer
❑ Retail Pharmacy	❑ Supermarket/Open Market
❑ Wholesale Pharmacy	❑ Family/Neighbour
❑ ADDO Shop	❑ Others, please specify……

VII. REPORTER NAME AND CONTACT ADDRESS	
Name: (Optional):	Contact Address:
Contact Phone No: _____	
E-mail: (if available) _____	
Date of this report: _____	
Thank you for your cooperation	***Ref No. (for official use)***

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ANNEX VI :

TFDA Tanzania Food & Drugs Authority	**PATIENT ADR ALERT CARD**	***TFDA/DMC/CTP/F/015*** ***Rev #:0***

Front side

ADVERSE DRUG REACTION ALERT CARD

PATIENT NAME: ……
AGE: …… GENDER: ……
DATE ISSUED: ……ADDRESS: ……
SUSPECTED DRUG(S): ……
DESCRIPTION OF REACTION: ……
Other comments (if any): ……
……

Please carry this card with you at all times and remember to show it to your health care provider at each time of consultation	***Tafadhali hakikisha umebeba kadi hii kila wakati na kumbuka kumwonyesha mhudumu wa afya unapo pata matibabu***

P. O. Box 77150, EPI Mabibo, Off Mandela Road, Dar es Salaam, Tel: +255-22-2450512/2450751/ 2452108, Fax: +255-22-2450793, Website: **www.tfda.go.tz**, Email: info@tfda.go.tz, adr@tfda.go.tz

CRITERIA FOR ISSUE OF A PATIENT ALERT CARD *Rear side*

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 VII: Causality Assessment Criteria for Suspected ADRs

Term	Description	Comments
Certain	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.	It is recognized that this stringent definition will lead to very few reports meeting the criteria, but this is useful because of the special value of such reports. It is considered that time relationships between drug administration and the onset and course of the adverse event are important in causality analysis. So also is the consideration of confounding features, but due weight must placed on the known pharmacological and other characteristics of the drug product being considered. Sometimes the clinical phenomena

		described will also be sufficiently specific to allow a confident causality assessment in the absence of confounding features and with appropriate time relationships, e.g. penicillin anaphylaxis.
Probable / Likely	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.	This definition has less stringent wording than for "certain" and does not necessitate prior knowledge of drug characteristics or clinical adverse reaction phenomena. As stated no re-challenge information is needed, but confounding drug administration underlying disease must be absent.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.	This is the definition to be used when drug causality is one of other possible causes for the described clinical event.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.	This definition is intended to be used when the exclusion of drug causality of a clinical event seems most plausible.
Conditional / Unclassified	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper	

	assessment or the additional data are under examination.	
Unassessable / Unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.	

Annex VIII: Pharmacovigilance Indicators

Definition

Indicators are specific objective measures that allow the evaluation of baseline situation and progress in healthcare services and interventions. In essence the pharmacovigilance (PV) performance indicators are measures of inputs, processes, outputs, outcomes, and impacts for PV programs or strategies. They are measures that describe how well a PV program is achieving its objectives. The set of PV indicators include a background information and three other categories of indicators – structural, process and outcome/impact

The following table explains in details M&E indicators for pharmacovigilance.

Pharmacovigilance Indicators

NMRA or PV Unit

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
Component 1. Policy, Law, and Regulation					
1.1	C	S	Existence of a policy document that contains essential statements on pharmacovigilance or safety of medicines, health products and technologies (stand alone or as a part of some other policy document)	3 years	Is there a national policy on pharmacovigilance or medicine safety, or a more general medicines policy that contains essential statements? When was the policy last reviewed? *Request documentation to verify.*
1.2	C	S	Existence of specific legal provisions for pharmacovigilance in the national medicines legislation or similar legislation	3 years	Are there legal provisions for pharmacovigilance or medicine safety in the medicines act or law? *Request documentation to verify.*

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
1.3	C	S	Legal provisions for Marketing Authorization Holders to monitor and report the safety and quality of their products	3 years	Is it mandatory by law or regulations for marketing authorization holders to conduct post marketing safety activities? *Request documentation to verify.* Is it mandatory by law or regulations for marketing authorization holder to report adverse drug reactions/medicine safety related issues? *Request documentation to verify.*
1.4	C	S	Existence of updated National Essential Medicines List that was reviewed with consideration of medicine safety information	3 years	Is there an essential medicines list in use? Does the essential medicines list selection committee consult medicine safety information? When was the list last reviewed? *Request documentation to verify.*
Component 2. Systems, Structures, and Stakeholder Coordination					
2.1	C	S	Existence of a national pharmacovigilance center with a clear mandate and structure	3 years	Is there a National pharmacovigilance center or any other body assigned the responsibility of monitoring safety of medicines? Is there a clear mandate and organizational structure for the pharmacovigilance center? *Request documentation to verify.* What is the organizational affiliation of the PV Center/Unit? (e.g. University, hospital pharmacy department, NMRA etc.)
2.2	C	S	The pharmacovigilance center has designated, qualified human resources to carry-out its functions	Annual	How many staff members (full-time equivalent) does the PV center have who are specifically responsible for carrying out its functions (technical and administrative)? *Request documentation to verify.*

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
					Do the technical staff in the pharmacovigilance center have professional or educational qualifications related to medicine, pharmacy/pharmaceutical, or related field (e.g. epidemiology, public health)?
2.3	C	S	Existence of a dedicated financial provision or statutory budget for the pharmacovigilance center	Annual	Is there an annual budgetary allocation for pharmacovigilance activities or for the Pharmacovigilance Center? In the last fiscal year, how many funds were allocated by the MOH and donors for pharmacovigilance activities? *Please enter the amount in the Answer box and specify the currency in the Notes column. Request documentation to verify.*
2.4	C	S	Existence of a functional national medicine safety advisory committee	Annual	Does a national medicine safety advisory committee exist with the responsibility to provide technical advice on the safety of medicines to the regulatory authority? Has the national medicine safety advisory committee met at least twice in the previous 12 months? *Request documentation to verify.*
2.5	C	S	Existence of national pharmacovigilance guidelines developed or reviewed within the past 5 years	3 years	Does a national guideline for pharmacovigilance (or a related document) exist? Has the national pharmacovigilance guideline been developed or reviewed within the past 5 years? When were the guidelines last reviewed? *Request documentation to verify.*

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
2.6	C	S	Existence of standard operating procedures (SOPs) for conducting pharmacovigilance activities	Annual	Does the NMRA have SOPs for pharmacovigilance activities? When were the SOPs last reviewed? *Request documentation to verify.*
2.7	C	S	Existence of a mechanism to disseminate pharmacovigilance information (including one or more of the following: newsletters, information bulletin, website or phone line for dissemination of pharmacovigilance information)	Annual	Is there a mechanism in place to disseminate PV information? Is there a newsletter or information bulletin for dissemination of PV information? *Request documentation to verify.* Is there a website for dissemination of PV information? Is there a publicly advertised phone line to receive and provide medicine safety and PV information? Is there another mechanism for dissemination of PV information? *Please describe the mechanism in Notes*
2.8	C	S	Existence of harmonized pharmacovigilance curricula for key healthcare workers - **Pre-Service**	3 years	Is PV incorporated into the national **pre-service** curricula of **doctors?** *Request documentation to verify.* Is PV incorporated into the national **pre-service** curricula of **nurses?** *Request documentation to verify.* Is PV incorporated into the national **pre-service** curricula of **pharmacists?** *Request documentation to verify.* Is the curriculum in use for **pre-service** training of healthcare workers the EAC harmonized PV curriculum? *Request documentation to verify.*

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
2.9	C	S	Existence of harmonized pharmacovigilance curricula for key healthcare workers - **In-Service**	3 years	Is there a pharmacovigilance training module, manual, or curriculum for **in-service** training of health care workers? *Request documentation to verify.* Is the curriculum in use for **in-service** training of healthcare workers the EAC harmonized PV curriculum? *Request documentation to verify.*
2.10	C	P	Number of healthcare workers trained in pharmacovigilance in the previous 12 months through in-service training program	Annual	How many healthcare workers has the center/program trained on PV in the previous 12 months (through **in-service** training)? *Request documentation to verify.* How many training events/sessions were conducted in the previous 12 months? *Request documentation to verify.*
2.11	C	S	Existence of a functioning platform, mechanism or strategy for the coordination of pharmacovigilance activities - **National Level**	Annual	Does a platform, mechanism or strategy for the coordination of pharmacovigilance activities (such as PV technical working group, forum or regularly scheduled meetings) exist among **national stakeholders**? Have the key **national stakeholders** been convened at least once in the previous 12 months? *Request documentation to verify.*
2.12	C	S	Existence of a functioning platform, mechanism or strategy for the coordination of pharmacovigilance activities – **EAC Regional Level**	Annual	Does a platform, mechanism or strategy for the coordination of pharmacovigilance activities (such as PV technical working group, forum or regularly scheduled meetings) exist among **EAC stakeholders**? Have the key **EAC stakeholders** been convened at least once in the previous 12 months? *Request documentation to verify.* Has the NMRA/PV center participated in at least one EAC stakeholder meeting in the previous 12 months? *Request documentation to verify.*

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
2.12	S	S	Evidence of a linkage between the Medicines Safety Committee and EAC Pharmacovigilance risk assessment advisory committee (PRAAC)	3 years	Is there information exchange and sharing between the National Medicines and Therapeutics Committee with the EAC Pharmacovigilance Risk Assessment and Advisory Committee? *Request documentation to verify.*
2.14	S	S	Adoption and use of harmonized web-based pharmacovigilance training tools	3 years	Does the national pharmacovigilance center offer the EAC web-based pharmacovigilance training tools?
2.15	S	P	Evidence of consideration of safety data when developing and updating standard treatment guidelines	3 years	Are pharmacovigilance data considered when developing standard treatment guidelines? *Request documentation to verify.*
2.16	C	S	National pharmacovigilance center is a full or associate member of the WHO Program for International Drug Monitoring	Annual	Is the national pharmacovigilance center a full or associate member of the WHO Program for International Drug Monitoring?
Component 3. Signal Generation and Data Management					
3.1	C	S	Existence of a national database for pharmacovigilance information	Annual	Does a central database exist for managing PV data? Does the central database contain data from various PV sources and methods? *Request documentation to verify.*

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
3.2	C	P	Evidence of a process or mechanism for sharing information with other regulatory functions, other regulatory agencies and global databases	Annual	Has information in the database been shared (either electronically or via report) with other regulatory functions, other regulatory agencies and/or global databases? *Request documentation to verify.*
3.3	C	S	Existence of a standard adverse event (AE) reporting form Subset indicators: The standard reporting form, or separate forms, provide for reporting of— - Adverse drug reactions - Suspected medication errors - Therapeutic ineffectiveness - Suspected misuse, abuse of and/or dependence on medicines - Adverse events following immunization (AEFI) - Medical devices and diagnostics	Annual	Is there a standard AE reporting form? *Request documentation to verify.* Are there relevant fields in the standard AE form (or a separate form) to report adverse drug reactions? Are there relevant fields in the standard AE form (or a separate form) to report suspected medication errors? Are there relevant fields in the standard AE form (or a separate form) to report therapeutic ineffectiveness? Are there relevant fields in the standard AE form (or a separate form) to report suspected misuse, abuse and/or dependence on medicines? Are there relevant fields in the standard AE form (or a separate form) to report AEFIs? Are there relevant fields in the standard AE form (or a separate form) to report adverse events related to medical devices and diagnostics?

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
3.4	C	S	Existence of a form (or section of ADE form) for reporting suspected product quality issues	Annual	Is there a form with relevant fields for reporting suspected/ observed poor quality issues? *Request documentation to verify.*
3.5	S	S	Existence of a form or mechanism for the public to report AEs (Patient reporting system)	Annual	Is there a standard reporting form for the general public to report AEs?
3.6	S	S	Existence of electronic AE reporting system that complies with international reporting format standards	3 years	Is there an electronic AE reporting system? Is the system compliant with the international reporting standards (E2B)?
Component 4. Risk Assessment and Evaluation					
4.1	C	P	Total number of AE reports received in the previous 12 months (also expressed as number of AEs per 100 000 persons in the population) Sub-indicators: - ADR - Suspected medication errors - Therapeutic ineffectiveness	Annual	What is the total number of AE reports received in the previous 12 months? *Request documentation to verify.* Of the total, what is the number of reports of ADR? Of the total, what is the number of reports of suspected medication errors? Of the total, what is the number of reports of therapeutic ineffectiveness?

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
			- Suspected misuse, abuse, dependence - AEFI - AE related to medical devices and diagnostics		Of the total, what is the number of reports of suspected misuse, abuse, dependence?
					Of the total, what is the number of reports of AEFI?
					Of the total, what is the number of reports of AE related to medical devices and diagnostics?
					What is the total population of the country?
4.2	C	P	Number and percentage of total AE reports received by the national pharmacovigilance center in the previous 12 months from: - Marketing Authorization Holders - PHPs - Health care providers - Patients	Annual	What is the number of AE reports received by the national pharmacovigilance center in the previous 12 months from marketing authorization holders?
					What is the number of AE reports received by the national pharmacovigilance center in the previous 12 months from public health programs?
					What is the number of AE reports received by the national pharmacovigilance center in the previous 12 months from healthcare providers?
					What is the number of AE reports received by the national pharmacovigilance center in the previous 12 months from patients?
					What is the total number of AE reports received in the previous 12 months?
4.3	C	P	Number and percentage of total AE reports received that are entered in the national database in the previous 12 months	Annual	What is the total number of ADE reports received that have been entered in the national database in the previous 12 months?

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
					What is the total number of ADE reports received in the previous 12 months?
4.4	C	P	Number and percentage of safety reports received at national level that have been submitted to the EAC regional database in the previous 12 months	Annual	What is the total number of AE reports that have been entered in the EAC database in the previous 12 months? *Request documentation to verify.*
					What is the total number of AE reports received in the previous 12 months?
4.5	C	P	Number and percentage of total AE reports acknowledged and/or issued feedback in the previous 12 months	Annual	What is the total number of AE reports acknowledged/issued feedback in the previous 12 months?
					What is the total number of AE reports received in the previous 12 months?
4.6	C	P	Number and percentage of ADE reports subjected to causality assessment in the previous 12 months	Annual	What is the total number of AE reports subjected to causality assessment in the previous 12 months?
					What is the total number of ADE reports received in the previous 12 months?
4.7	C	P	Number and percentage of ADE reports committed to VigiBase in the previous 12 months	Annual	How many of the ADE reports received at the national pharmacovigilance center were committed to Vigibase in the previous 12 months?
					What is the total number of ADE reports received in the previous 12 months?
4.8	C	P	Average completeness score of quarterly reports committed to VigiBase in the previous four quarters (= one year)	Annual	What was the average completeness score of quarterly reports committed to Vigibase in the previous four quarters? *Consult quarterly reports from VigiGrade for completeness scores of submitted reports*

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
4.9	C	P	Number of active surveillance activities initiated, ongoing or completed during the previous three years	3 years	How many active surveillance studies have been conducted in the last three years (36 months)? Indicate what type (e.g. cohort event monitoring, targeted spontaneous reporting, etc.) and stage of completion (e.g. initiated, on-going or completed) for each study. *Request documentation to verify.*
4.10	S	P	Number and percentage of total AE reports received at the national pharmacovigilance center in the previous 12 months from healthcare providers by type of provider	Annual	What is the number of AE reports received in the previous 12 months submitted by **doctors**? What is the number of AE reports received in the previous 12 months submitted by **nurses**? What is the number of AE reports received in the previous 12 months submitted by **pharmacists**? What is the total number of AE reports received in the previous 12 months?
4.11	S	P	Evidence of supervision visits to marketing authorization holders by NMRA that address	Annual	Does the NMRA conduct supervision visits of MAHs that address PV?

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
			PV		How many supervision visits have been conducted in the previous 12 months?
Component 5. Risk Management and Communication					
5.1	C	O	Number of regulatory actions taken in the previous 12 months as a consequence of national pharmacovigilance activities including: - Number of product label changes (variation); - Number of safety warnings on medicines to health professionals and general	Annual	How many regulatory actions were taken in the preceding 12 months as a consequence of pharmacovigilance activities that resulted in ***product label changes (variation)***? How many regulatory actions were taken in the preceding 12 months as a consequence of pharmacovigilance activities that resulted in ***safety warnings on medicines to health professionals***?

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
			public; - Number of withdrawals of medicines; - Number of other restrictions on use of medicines; - Number of treatment guideline/policy changes *Request documentation to verify.*		How many regulatory actions were taken in the preceding 12 months as a consequence of pharmacovigilance activities that resulted in ***safety warnings on medicines to the general public***? How many regulatory actions were taken in the preceding 12 months as a consequence of pharmacovigilance activities that resulted in ***withdrawals of medicines***? How many regulatory actions were taken in the preceding 12 months as a consequence of pharmacovigilance activities that resulted in ***treatment guideline/policy changes***? How many regulatory actions were taken in the preceding 12 months as a consequence of pharmacovigilance activities that resulted in ***other restrictions on use of medicines***?
5.2	C	O	Number of signals detected in the past 3 years by the pharmacovigilance center	3 years	How many signals were detected in the past 3 years by the pharmacovigilance center?
5.3	S	O	Average time lag between identification of safety signal of a serious ADR or significant medicine safety issue generated nationally and communication to health care workers and the public	Annual	How long does it take from when a safety signal or significant safety issue is identified to when it is communicated to health workers and the public? *Please answer in days.*
5.4	S	O	Number of suspected product quality issues detected through the pharmacovigilance system	Annual	What is the number of suspected product quality issues detected through the pharmacovigilance system in the previous 12 months? *Request documentation to verify.*

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
5.5	S	O	Percentage of planned issues of the medicine safety bulletin (or any other health-related newsletter that routinely features ADR or medicine safety issues) published in the previous 12 months	Annual	How many issues of the medicine safety bulletin are supposed to be published per year? How many issues of the medicine safety bulletin were published in the previous 12 months? *Request documentation to verify.*
5.6	S	O	Number of products voluntarily withdrawn by marketing authorization holders because of safety concerns in the previous 12 months	Annual	How many products were voluntarily withdrawn by marketing authorization holders because of safety concerns in the previous 12 months?
5.7	S	O	Number and percentage of medicine safety information requests addressed in the previous 12 months	Annual	How many requests for information about medicine safety were received in the previous 12 months? *Request documentation to verify.* Of the total received, how many requests for medicine safety information were addressed in the previous 12 months?
5.8	S	O	Number of medicine safety issues of local relevance identified from outside sources (e.g., from another country, from EAC region or international sources) and acted on locally in the previous 12 months	Annual	How many medicine safety issues identified from outside sources were acted on locally in the previous 12 months? *Request documentation to verify.*
5.9	S	O	Number of public or community education activities relating to medicine safety carried out in the previous 12 months	Annual	How many public or community education activities relating to medicine safety were carried out in the previous 12 months? *Request documentation to verify.*

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
Component 1. Policy, Law, and Regulation					
Component 2. Systems, Structures, and Stakeholder Coordination					
P2.1	C	P	Pharmacovigilance activities included within the strategic and/or annual operational plans of public health programs	Annual	Are pharmacovigilance activities included within the strategic and/or annual operational plans of public health programs? *Request documentation to verify.*
P2.2	C	S	Existence of a dedicated financial provision or statutory budget for the PHPs	Annual	Is there an annual budgetary allocation for pharmacovigilance activities for the PHP? *Request documentation to verify.* In the last fiscal year, how many funds were allocated by the MOH and donors for pharmacovigilance activities? *Please enter the amount in the Answer box and specify the currency in the Notes column.*
P2.3	C	S	Existence of a mechanism to disseminate pharmacovigilance information (including	Annual	Is there a mechanism in place to disseminate PV information?

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
			one or more of the following: newsletters, information bulletin, website or phone line for dissemination of pharmacovigilance information)		Is there a newsletter or information bulletin for dissemination of PV information? *Request documentation to verify.*
					Is there a website for dissemination of PV information?
					Is there a publicly advertised phone line to receive and provide medicine safety and PV information?
					Is there another mechanism for dissemination of PV information? *Please describe the mechanism*
P2.4	C	P	Number of healthcare workers trained in pharmacovigilance in the previous 12 months through in-service training	Annual	How many healthcare workers has the center/program trained on PV in the previous 12 months (through **in-service** training)? *Request documentation to verify.*
					How many training events/sessions were conducted in the previous 12 months? *Request documentation to verify.*
P2.5	C	P	Number of national treatment guidelines or protocols in use within the public health programs that consider pharmacovigilance	Annual	Do the treatment guidelines or protocols in use in the PHP provide instruction for PV activities? *Request documentation to verify.*
P2.6	S	P	Evidence of consideration of safety data when developing and updating standard treatment guidelines or treatment policies	3 years	Are pharmacovigilance data considered when developing standard treatment guidelines? *Request documentation to verify.*
Component 3. Signal Generation and Data Management					
P3.1	C	P	PHPs use the national, standard ADR/AE reporting form	Annual	Does the PHP use the national, standard ADR/AE reporting form?

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
Component 4. Risk Assessment and Evaluation					
P4.1	C	P	Number and percentage of ADR/AE reports received by PHPs that were submitted to the national pharmacovigilance center in the previous 12 months	Annual	What is the number of AE reports received by the PHP in the previous 12 months? What is the number of AE reports submitted by the PHP to the national PV center in the previous year?
P4.2	C	P	Number of active surveillance activities initiated, ongoing or completed during the past three years	3 years	How many active surveillance studies have been conducted in the last three years (36 months)? Indicate what type (e.g. cohort event monitoring, targeted spontaneous reporting, etc.) and stage of completion (e.g. initiated, on-going or completed) for each study *Request documentation to verify*
P4.3	S	O	Percentage of patients in public health programs for whom drug-related, serious unexpected adverse events were reported in the previous 12 months	Annual	What is the total number of patients receiving medicines under the PHP? *Request documentation to verify.* What is the total number of patients receiving medicines in the PHP who experienced drug-related, serious, unexpected adverse events? *Request documentation to verify.* How many of those were reported to the national PV center? *Request documentation to verify.*
Component 5. Risk Management and Communication					

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
P5.1	S	O	Average time lag between identification of safety signal of a serious ADR or significant medicine safety issue generated nationally and communication to health care workers and the public	Annual	How long does it take from when a safety signal or significant safety issue is identified to when it is communicated to health workers and the public? *Please enter your answer in days.*
P5.2	S	O	Number of suspected product quality issues detected through public health programs	Annual	What is the number of suspected product quality issues detected through the PHP in the previous 12 months?
P5.3	S	O	Existence of a program-related newsletter that routinely features ADR or medicine safety information	Annual	Is there a program-related newsletter, bulletin or other publication that routinely features ADR or medicine safety information?
P5.4	S	O	Number and percentage of medicine safety information requests addressed in the previous 12 months	Annual	How many requests for information about medicine safety were received in the previous 12 months? *Request documentation to verify.* How many requests for medicine safety information were addressed in the previous 12 months? *Request documentation to verify.*
P5.5	S	O	Number of medicine safety issues of local relevance identified from outside sources (e.g., from another country, from EAC region or international sources) and acted on locally in the previous 12 months	Annual	How many medicine safety issues identified from outside sources were acted on locally in the previous 12 months? *Request documentation to verify.*
P5.6	S	O	Number of public or community education activities relating to medicine safety carried out in the previous 12 months	Annual	How many public or community education activities relating to medicine safety were carried out by the PHP in the previous 12 months? *Request documentation to verify.*

Health Facilities

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
Component 1. Policy, Law, and Regulation					
Component 2. Systems, Structures, and Stakeholder Coordination					
F2. 1	C	S	Existence of a mechanism to disseminate pharmacovigilance information (including one or more of the following: newsletters, information bulletin, website or phone line for dissemination of pharmacovigilance information)	Annual	Is there a mechanism in place to disseminate PV information in your health facility?
					Is there a newsletter or information bulletin for dissemination of PV information? *Request documentation to verify.*
					Is there a website for dissemination of PV information?
					Is there a publicly advertised phone line to receive and provide medicine safety and PV information?
					Is there another mechanism for dissemination of PV information? *Please describe the mechanism in Notes*
F2. 2	C	P	Number of healthcare workers trained in pharmacovigilance in the previous 12 months through **in-service** training	Annual	How many healthcare workers has the facility trained on PV in the previous 12 months (through **in-service** training)? *Request documentation to verify.*
					How many training events/sessions were conducted in the previous 12 months? *Request documentation to verify.*
Component 3. Signal Generation and Data Management					

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
F3.1	S	P	Percentage of surveyed healthcare facilities with functional pharmacovigilance (submitted >10 ADE reports to the national pharmacovigilance center in the previous 12 months) (Facility level: Healthcare facility submitted >10 AE reports to the national pharmacovigilance center in the previous 12 months)	Annual	How many AE reports did the health facility submit to the national pharmacovigilance center in the previous 12 months?
Component 4. Risk Assessment and Evaluation					
Component 5. Risk Management and Communication					
F5.1	S	O	Percentage of surveyed health facilities that has Drug and Therapeutics Committees that have carried out pharmacovigilance activities or addressed medicine safety issues in the previous 12 months	Annual	Does the health facility have a Drug and Therapeutics Committee? Within the previous 12 months, has the DTC carried out any pharmacovigilance activities or addressed medicine safety issues? *Request documentation to verify.*
F5.2	S	O	Number of suspected product quality issues detected through surveyed health facilities	Annual	What is the number of suspected product quality issues detected at the health facility e in the previous 12 months?
F5.3	S	O	Number and percentage of medicine safety information requests addressed in the previous 12 months	Annual	How many requests for information about medicine safety were received in the previous 12 months? *Request documentation to verify.* How many requests for medicine safety information were addressed in the previous 12 months? *Request documentation to verify.*

Indicator #	Core or Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
F5.4	S	O	Number of public or community education activities relating to medicine safety carried out in the previous 12 months	Annual	How many public or community education activities relating to medicine safety were carried out by the health facility in the previous 12 months?

Marketing Authorization Holders

Indicator #	Supplementary	Indicator Type	Indicator	Collection Frequency	Assessment Questions
Component 1. Policy, Law, and Regulation					
Component 2. Systems, Structures, and Stakeholder Coordination					
M2.1	S	S	Percentage of surveyed marketing authorization holders that has a designated qualified (QPV) pharmacovigilance person (MAH: Existence of a qualified pharmacovigilance person at the MAH)	Annual	Is there a designated qualified pharmacovigilance person (QPV) at the company? *Request documentation to verify.*
Component 3. Signal Generation and Data Management					
Component 4. Risk Assessment and Evaluation					
M4.1	S	S	Percentage of surveyed marketing authorization holders that have procedures for the collection and reporting of safety issues (e.g. ICSRs and PSURs) to the NMRA	Annual	Does the marketing authorization holder have procedures in place for collecting and reporting safety issues to the NMRA? *Request documentation to verify*
Component 5. Risk Management and Communication					
M5.1	S	O	Number and percentage of risk mitigation plans currently in place that are targeted at high-risk medicines that have been submitted to the NMRA	Annual	Does the MAH have any risk mitigation plans currently in place for high-risk medicines? How many risk mitigation plans are in place? How many risk mitigation plans have been submitted to the NMRA?

Annex 9: Summary of Expedited ADR Reporting requirements to the Authority (Timeline for ADR Reporting)

Reporter Category	**Types of Adverse Reaction**	**Time Frame for Reporting**	**Other Action to be taken**
Healthcare Professional	Serious with fatal or life threatening outcome	As soon as possible, but no later than 7 calendar days, after first knowledge of the case. This report should include the assessment from the investigation and other relevant document.	
	Serious but there are no life threatening or fatal outcome	As soon as possible but no later than 15 calendar days after first knowledge of the case.	
	Non-serious	As soon as possible after first knowledge of the case	
Product Registration Holder	**Local report**		
	Serious (expected or unexpected) with fatal or life threatening outcome	As soon as possible, but no later than 7 calendar days, after first knowledge by PRH, followed by complete report within 8 calendar days. This report should include the assessment from the investigation and other relevant document.	
	Serious, expected or unexpected but there are no life threatening or fatal outcome.	As soon as possible but no later than 15 calendar days after first knowledge by registration holder.	
	Non-serious, expected or unexpected	Within 30 calendar days	
	Foreign reports		
	Individual case report	Not required on routine basis	
	Notification of any significant safety issue such as new information impacting on risk(s) benefit profile of medicinal product including international regulatory	No later than 3 calendar days	

	decision or action		
	Withdrawal/suspension of registration in any country	24 hours after first knowledge by registration holder	
Market Authorization Holder	All adverse events	Provide information to TFDA on all adverse Drug reactions, Submit report on adverse reactions occurring outside Tanzania	Inform TFDA on any significant safety issue(s) or action(s) taken by foreign agency, including the basis for such action(s), and Provide periodic safety update report(s) (PSURs) for the marketed product Submit risk management plans including risk-benefit assessment reports to TFDA. Monitor the outcome of measures to reduce risks to a minimum under the plan of risk management Implement a system of risk management for any medicine.

			Notify the TFDA of any action to withdraw a product from the market (to suspend marketing, to withdraw from market, to request withdrawal of a market authorisation, or not to apply for a renewal of a market authorization),
	No adverse events	Submit a "null" six monthly report for the first two years and annually for the following three years if there is no ADR report submitted to them	

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